10/ 075,073

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NEWS 4	DEC 08	INPADOC: Legal Status data reloaded
NEWS 5	SEP 29	DISSABS now available on STN
NEWS 6	OCT 10	PCTFULL: Two new display fields added
NEWS 7	OCT 21	BIOSIS file reloaded and enhanced
NEWS 8	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
NEWS 9	NOV 24	MSDS-CCOHS file reloaded
NEWS 10	DEC 08	CABA reloaded with left truncation
NEWS 11	DEC 08	IMS file names changed
NEWS 12	DEC 09	Experimental property data collected by CAS now available in REGISTRY
NEWS 13	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAplus
NEWS 14	DEC 17	DGENE: Two new display fields added
NEWS 15	DEC 18	BIOTECHNO no longer updated
NEWS 16	DEC 19	CROPU no longer updated; subscriber discount no longer available
NEWS 17	DEC 22	Additional INPI reactions and pre-1907 documents added to CAS databases
NEWS 18	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
NEWS 19	DEC 22	ABI-INFORM now available on STN
NEWS 20	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 21	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS 22	FEB 05	German (DE) application and patent publication number format changes
NEWS 23	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS 24	MAR 03	MEDLINE file segment of TOXCENTER reloaded
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FILE 'HOME' ENTERED AT 14:29:28 ON 15 MAR 2004

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'CAPLUS' ENTERED AT 14:29:37 ON 15 MAR 2004

FILE COVERS 1907 - 15 Mar 2004 VOL 140 ISS 12
FILE LAST UPDATED: 14 Mar 2004 (20040314/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s "MMP-13" or metaloprotease
          8841 "MMP"
        737863 "13"
           663 "MMP-13"
                 ("MMP"(W)"13")
             2 METALOPROTEASE
L1         665 "MMP-13" OR METALOPROTEASE

=> s "MMP-13" or metaloprotease?
          8841 "MMP"
        737863 "13"
           663 "MMP-13"
                 ("MMP"(W)"13")
             4 METALOPROTEASE?
L2         667 "MMP-13" OR METALOPROTEASE?

=> s l2 and (cancer? or heart? or inflammation or arthritis)
        220765 CANCER?
        307476 HEART?
        103679 INFLAMMATION
         31884 ARTHRITIS
L3         278 L2 AND (CANCER? OR HEART? OR INFLAMMATION OR ARTHRITIS)

=> s l3 not py>2000
       3194430 PY>2000
L4          64 L3 NOT PY>2000
```

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=> d l4 1- ibib abs
YOU HAVE REQUESTED DATA FROM 64 ANSWERS - CONTINUE? Y/(N):y

L4 ANSWER 1 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:193611 CAPLUS
DOCUMENT NUMBER: 135:150745
TITLE: Specific expression of matrix metalloproteinases 1, 3, 9 and 13 associated with invasiveness of breast **cancer** cells in vitro
AUTHOR(S): Balduyck, Malika; Zerimech, Farid; Gouyer, Valerie; Lemaire, Raphael; Hemon, Brigitte; Grard, Georges; Thiebaut, Carole; Lemaire, Veronique; Dacquembronne, Evelyne; Duhem, Therese; Lebrun, Anne; Dejonghe, Marie-Jose; Huet, Guillemette
CORPORATE SOURCE: Laboratoire de Biochimie, Hopital Claude Huriez, Lille, 59037, Fr.
SOURCE: Clinical & Experimental Metastasis (2000), 18(2), 171-178
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) were studied in highly invasive (MDA-MB-231) and slightly invasive (MCF-7, T47D, BT-20) breast **cancer** cell lines. Investigations were carried out at the protein level and/or at the mRNA level, either in cells cultured as monolayers on plastic, or in cells seeded on a thin layer of Matrigel basement membrane matrix. Anal. of MMP expression by RT-PCR showed expression of MMP-1, MMP-3, and **MMP-13** in highly invasive MDA-MB-231 cells, but not in slightly invasive cell lines. The extracellular secretion of MMP-1 and MMP-3 by MDA-MB 231 cells could be also shown by ELISA. TIMP-1 and TIMP-2 mRNAs were found in all cell lines, however, the extracellular secretion of both TIMPs was much higher in MDA-MB-231 cells than in the other cell lines. When the cells were cultured on Matrigel matrix, MMP-9 expression was induced in MDA-MB-231 cells only, as assessed by RT-PCR and zymog. expts. The invasive potential of MDA-MB-231 cells evaluated in vitro through Matrigel was significantly inhibited by the MMP inhibitor BB-2516, by 25% and 50% at the concns. of 2 + 10-6 M and 10-5 M, resp. In conclusion,these data show that highly invasive MDA-MB-231 cells but not slightly invasive T47D, MCF-7 and BT-20 cells express MMP-1, MMP-3, MMP-9 and **MMP-13**, MMP-9 which is specifically up-regulated by cell contact to Matrigel, may play a key role in the invasiveness of MDA-MB-231 cells through basement membranes.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:83371 CAPLUS
DOCUMENT NUMBER: 135:17612
TITLE: Interstitial collagenases as markers of tumor progression
AUTHOR(S): Brinckerhoff, Constance E.; Rutter, Joni L.; Benbow, Ulrike
CORPORATE SOURCE: Department of Medicine, Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Clinical Cancer Research (2000), 6(12), 4823-4830
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 102 refs. Degradation of the extracellular matrix is the sine qua non of tumor invasion and metastasis. Most of this degradation is

mediated by matrix metalloproteinases (MMPs), a family of enzymes that, collectively, degrades the extracellular matrix. Although the basement membrane-degrading enzymes, MMP-2 and MMP-9, were given considerable attention for their roles in invasion and metastasis, the interstitial collagenases, a subfamily of MMPs that cleaves the stromal collagens types I and III, have received relatively little recognition for their part in these processes. This subfamily is comprised of collagenase 1 (MMP-1), collagenase 3 (**MMP-13**), and the MT-MMPs, membrane-bound MMPs, and numerous reports over the last several years document the expression of these MMPs in a wide variety of advancing tumors. Of particular interest is a single nucleotide polymorphism in the MMP-1 promoter that increases the transcription of this gene and that is associated with melanoma and with ovarian and endometrial **cancers.** The collagenases can mediate tumor invasion through several mechanisms, which include constitutive production of enzyme by the tumor cells, induction of collagenase production in the neighboring stromal cells, and interactions between tumor/stromal cells to induce collagenase production by one or both cell types. Thus, evidence indicates that elevated expression of the interstitial collagenases is associated with a poor prognosis in a variety of **cancers**, and therefore, these MMPs can serve as a marker of tumor progression.

REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:857126 CAPLUS
TITLE: Cyclic sulphone MMP inhibitors
AUTHOR(S): Anon.
SOURCE: Expert Opinion on Therapeutic Patents (2000), 10(12), 1947-1950
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Matrix metalloproteinases (MMP) inhibitors have therapeutic potential in a variety of human diseases such as **cancer, arthritis** and multiple sclerosis. Over the last decade a large number of pharmaceutical companies have had active programs in the area resulting in several orally bioavailable MMP inhibitors advancing into clin. trials. This patent claims a structurally relatively unique series of MMP inhibitors based on a novel cyclic sulfone scaffold. Compds. within this application have promising in vitro profiles, with nM potency against **MMP-13**, however since there is no in vivo efficacy or pharmacokinetic data as of yet, it is not possible at this time to ascertain if this series will offer any advantage over the current series of inhibitors.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:848855 CAPLUS
DOCUMENT NUMBER: 134:54990
TITLE: Induction of collagenase-3 (**MMP-13**) in rheumatoid **arthritis** synovial fibroblasts
AUTHOR(S): Moore, Bryan A.; Aznavoorian, Sadie; Engler, Jeffrey A.; Windsor, L. Jack
CORPORATE SOURCE: Research Center in Oral Cancer, University of Alabama at Birmingham, Birmingham, AL, 35294, USA
SOURCE: Biochimica et Biophysica Acta (2000), 1502(2), 307-318
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.

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DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is a growing body of evidence that implicates matrix metalloproteinases (MMPs) as major players in numerous diseased conditions. The articular cartilage degradation that is characteristic of rheumatoid **arthritis** (RA) is believed to be mediated by the collagenase subfamily of matrix metalloproteinases. The preference of collagenase-3 (CL-3) for collagen type II makes it a likely candidate in the turnover of articular cartilage and a potential target for drug development. In this study, RA synovial membrane tissue was shown to express CL-3 mRNA by reverse transcriptase-polymerase chain reaction (RT-PCR) and protein by immunohistochem. Fibroblasts isolated and cultured from RA synovial membrane tissue were induced to express CL-3 mRNA. CL-3 mRNA was detected after PMA treatment in 16 of the 18 RA synovial membrane fibroblast cell lines established for this study. These fibroblasts also expressed mRNA for collagenase-1 (CL-1, MMP-1), membrane type-1 matrix metalloproteinase, gelatinase A, gelatinase B, stromelysin-1, stromelysin-2, TIMP-1, and TIMP-2. They were further shown to express CL-1 mRNA constitutively and CL-3 mRNA only after stimulation with PMA, IL-1, TGF-β1, TNF-α, or IL-6 with IL-6sR. These fibroblasts also expressed after induction both CL-1 and CL-3 at the protein level as determined by Western blot analyses and immunofluorescence.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:845510 CAPLUS
DOCUMENT NUMBER: 134:13035
TITLE: Inhibition of matrix metalloproteinases by bisphosphonates may in part explain their effects in the treatment of multiple myeloma
AUTHOR(S): Teronen, Olli; Laitinen, Minna; Salo, Tuula; Hanemaaijer, Roeland; Heikkila, Pia; Konttinen, Yrjo T.; Sorsa, Timo
CORPORATE SOURCE: Department of Oral and Maxillofacial Surgery Faculty of Medicine, Institute of Medical Technology, University of Tampere, Tampere, Finland
SOURCE: Blood (2000), 96(12), 4006-4007
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 13 refs. Identification of pharmacol. potential agents that inhibit human cell derived matrix metalloproteinase (MMP) has long seemed a reasonable therapeutic goal for modulation and down-regulation of metastases formation and bone destruction in many pathol. states. Our data show that clodronate (and several other bisphosphonates; data not shown) can inhibit in vitro the activities of **cancer**-related enzymes MMP-2, MMP-9, **MMP-13**, MT1-MMP (and several other MMPs). In our study with patients receiving clodronate therapy, a slight but significant decrease in the salivary collagenase level was observed after 3 wk, demonstrating a down-regulating effect of MMPs by clodronate in vivo. We propose that the beneficial effects of the bisphosphonates on the metastatic process may be related to inhibition and down-regulation of various genetically distinct MMPs that are crucial in the escape of malignant cells into and out of circulation, and destruction of local tissue at a metastatic site.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:798976 CAPLUS
DOCUMENT NUMBER: 134:55328

10/ 075,073

TITLE: Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase- and cathepsin-dependent emphysema
AUTHOR(S): Zheng, Tao; Zhu, Zhou; Wang, Zhongde; Homer, Robert J.; Ma, Bing; Riese, Richard J., Jr.; Chapman, Harold A., Jr.; Shapiro, Steven D.; Elias, Jack A.
CORPORATE SOURCE: Section of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, 06520-8057, USA
SOURCE: Journal of Clinical Investigation (2000), 106(9), 1081-1093
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cigarette smoke exposure is the major cause of chronic obstructive pulmonary disease (COPD). However, only a minority of smokers develop significant COPD, and patients with asthma or asthma-like airway hyperresponsiveness or eosinophilia experience accelerated loss of lung function after cigarette smoke exposure. Pulmonary **inflammation** is a characteristic feature of lungs from patients with COPD. Surprisingly, the mediators of this **inflammation** and their contributions to the pathogenesis and varied natural history of COPD are not well defined. Here the authors show that IL-13, a critical cytokine in asthma, causes emphysema with enhanced lung vols. and compliance, mucus metaplasia, and **inflammation**, when inducibly overexpressed in the adult murine lung. MMP-2, -9, -12, -13, and -14 and cathepsins B, S, L, H, and K were induced by IL-13 in this setting. In addition, treatment with MMP or cysteine proteinase antagonists significantly decreased the emphysema and **inflammation**, but not the mucus in these animals. These studies demonstrate that IL-13 is a potent stimulator of MMP and cathepsin-based proteolytic pathways in the lung. They also demonstrate that IL-13 causes emphysema via a MMP-and cathepsin-dependent mechanism(s) and highlight common mechanisms that may underlie COPD and asthma.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:777213 CAPLUS
DOCUMENT NUMBER: 134:69228
TITLE: Matrix metalloproteinases collagenase-2, macrophage elastase, collagenase-3, and membrane type 1-matrix metalloproteinase impair clotting by degradation of fibrinogen and factor XII
AUTHOR(S): Hiller, Oliver; Lichte, Andrea; Oberpichler, Andre; Kocourek, Andreas; Tschesche, Harald
CORPORATE SOURCE: Department of Biochemistry, Faculty of Chemistry, University of Bielefeld, Bielefeld, 33615, Germany
SOURCE: Journal of Biological Chemistry (2000), 275(42), 33008-33013
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of plasma proteins on controlling the activity of matrix metalloproteinases (MMPs, matrixins) have been the focus of numerous studies, although only a few have examined the influence of matrixins on plasma proteins. Recently, it has been shown that MMPs may play a role in the degradation of fibrin. We have now investigated the role of collagenase-2 (MMP-8), macrophage elastase (MMP-12), collagenase-3 (**MMP-13**), and membrane type 1-matrix metalloproteinase (MT1-MMP, MMP-14) in the degradation of fibrinogen and Factor XII of the plasma clotting

system. Our data demonstrate that the catalytic domains of MMP-8, MMP-12, **MMP-13**, and MMP-14 can proteolytically process fibrinogen and, with the exception of MMP-8, also inactivate Factor XII (Hageman factor). We have identified the amino termini of the major protein fragments. Cleavage of fibrinogen occurred in all chains and resulted in significantly impaired clotting. Moreover, rapid proteolytic inactivation of Factor XII (Hageman factor) by MMP-12, **MMP-13**, and MMP-14 was noted. These results support the hypothesis of an impaired thrombolytic potential of MMP-degraded Factor XII in vivo. MMP-induced degradation of fibrinogen supports a plasmin-independent fibrinolysis mechanism. Consequently, degradation of these proteins may be important in **inflammation**, atherosclerosis, and angiogenesis, all of which are known to be influenced by MMP activity.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:776208 CAPLUS
DOCUMENT NUMBER: 134:69817
TITLE: Retinoic acid combines with interleukin-1 to promote the degradation of collagen from bovine nasal cartilage: matrix metalloproteinases-1 and -13 are involved in cartilage collagen breakdown
AUTHOR(S): Shingleton, W. D.; Ellis, A. J.; Rowan, A. D.; Cawston, T. E.
CORPORATE SOURCE: Department of Rheumatology, The Medical School, University of Newcastle upon Tyne, NE2 4HH, UK
SOURCE: Journal of Cellular Biochemistry (2000), 79(4), 519-531
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Retinoic acid (RetA) and interleukin-1α (IL-1) together can induce a reproducible release of proteoglycan fragments from bovine nasal cartilage in culture. However, release of collagen fragments with either agent alone is often variable. In this study over 70% of the total collagen was released from bovine nasal cartilage in culture by day 14 when RetA and IL-1 were combined. This release was accompanied by the appearance of collagenolytic activity in the culture medium that cleaved collagen specifically at the 1/4/3/4 position. Tissue inhibitor of metalloproteinases (TIMP) activity was present at day 7 but low or absent in media from resorbing tissue at day 14. The breakdown of cartilage collagen could be prevented by the addition of BB-94, a specific metalloproteinase inhibitor. These results suggest that RetA promotes the early release of TIMP from the tissue and that IL-1 stimulates pro-collagenase secretion which, when activated, exceeds the local concentration of TIMP. Thus in the later stages of culture collagen destruction occurs. Both MMP-1 and **MMP-13** were detected and appear to be involved in IL-1 + RetA induced bovine cartilage destruction. However, for the first time, we also present evidence to suggest that **MMP-13** is the predominant collagenase in this system.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:611230 CAPLUS
DOCUMENT NUMBER: 133:279659
TITLE: Human keratinocyte cell lines differ in the expression of the collagenolytic matrix metalloproteinases-1, -8, and -13 and of TIMP-1
AUTHOR(S): Bachmeier, Beatrice E.; Nerlich, Andreas G.; Boukamp, Petra; Lichtinghagen, Ralf; Tschesche, Harald; Fritz,

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Hans; Fink, Edwin
CORPORATE SOURCE: Department of Clinical Chemistry and Clinical Biochemistry, University Hospital of Surgery, Ludwig-Maximilians-University, Munich, D-80336, Germany
SOURCE: Biological Chemistry (2000), 381(5/6), 509-516
CODEN: BICHF3; ISSN: 1431-6730
PUBLISHER: Walter de Gruyter GmbH & Co. KG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated cells and conditioned media of the three human keratinocyte cell lines HaCaT (non-tumorigenic), A5 (benign, tumorigenic) and II-4RT (malignant, tumorigenic) with regard to production and secretion of the collagenases-1 to -3 (MMP-1, MMP-8 and **MMP-13**) and TIMP-1 using semi-nested RT-PCR, Western blots, ELISA, immunocytochem. and casein zymog. Transcripts of MMP-1, -8, -13 and TIMP-1 were detected in all cell lines by RT-PCR and the corresponding proteins were found in the cytoplasm of all three cell lines by Western blot anal. and/or immunocytochem. The conditioned media of the malignant 11-4RT cells contain significantly more MMP-1 and MMP-8 than those of HaCaT or A5 as evidenced by immunoblotting and ELISA. In addition to the presence of latent MMP-1, zymog. also detected the active form of this enzyme. TIMP-1 was found only in exts. of all three cell lines, predominantly in A5. This study clearly indicates that the epithelial tumor cells synthesize different collagenases and TIMP-1. The malignant clone secretes increased amts. of distinct collagenases compared to the non-tumorigenic cell line, thereby verifying a correlation between biol. behavior and the amount of collagenases. In addition, we provide clear evidence that MMP-8 is not exclusively found in polymorphonuclear granulocytes, but also in keratinocyte cell lines.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:545049 CAPLUS
DOCUMENT NUMBER: 134:15894
TITLE: Increased expression of collagenase-3 (**MMP-13**) and MT1-MMP in esophageal **cancer** is related to **cancer** aggressiveness
AUTHOR(S): Etoh, T.; Inoue, H.; Yoshikawa, Y.; Barnard, G. F.; Kitano, S.; Mori, M.
CORPORATE SOURCE: Department of Surgery, Medical Institute of Bioregulation, Kyushu University, Beppu, Japan
SOURCE: Gut (2000), 47(1), 50-56
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Collagenase-3 (matrix metalloproteinase-13, **MMP-13**) is a recently identified human MMP with broad substrate specificity which can be activated by membrane type 1 (MT1) matrix metalloproteinase in vitro. These may play a critical role in **cancer** aggressiveness. To examine the clin. significance of collagenase-3 expression and the cooperative role of MT1-MMP in human esophageal carcinomas. Forty five individuals with esophageal carcinoma who underwent surgery without preoperative treatment. The tumor/normal (T/N) ratios of collagenase-3 and MT1-MMP mRNA expression in 45 human esophageal carcinomas were determined by northern blot anal. The production and localisation of collagenase-3 and MT1-MMP proteins were investigated by immunohistochem., western blot anal., and zymog. The mean T/N ratio of collagenase-3 mRNA was 3.5 and that of MT1-MMP 2.1. There was a significant correlation between collagenase-3 and MT1-MMP mRNA expression ($p<0.001$). Twenty two cases with a collagenase-3 T/N ratio >3.5 showed a significantly higher

frequency of vascular involvement and lymph node metastasis, and tended to be at a more advanced stage than 23 cases with a T/N ratio 3.5 ($p<0.05$). Western blot anal. and zymog. demonstrated production of collagenase-3 protein in tumor tissues but not in normal tissues. Immunohistochem. studies revealed that collagenase-3 was localised predominantly in tumor cells and MT1-MMP was detected in the same collagenase-3 pos. cells; there was a significant association between collagenase-3 and MT1-MMP protein expression ($p<0.05$). With regard to prognosis, the survival time for subjects in the high collagenase-3 group (T/N ratio >3.5) was significantly worse ($p<0.05$). These data suggest that production of collagenase-3 together with MT1-MMP is implicated in tumor aggressiveness and prognosis in human esophageal carcinomas.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:491483 CAPLUS
DOCUMENT NUMBER: 133:348674
TITLE: Differential expression pattern of membrane-type matrix metalloproteinases in rheumatoid **arthritis**
AUTHOR(S): Pap, Thomas; Shigeyama, Yukio; Kuchen, Stefan; Fernihough, Janet K.; Simmen, Beat; Gay, Renate E.; Billingham, Michael; Gay, Steffen
CORPORATE SOURCE: WHO Collaborating Center for Molecular Biology and Novel Therapeutic Strategies for Rheumatic Diseases, University Hospital, Zurich, Switz.
SOURCE: Arthritis & Rheumatism (2000), 43(6), 1226-1232
CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: to study the expression of mRNA for different membrane-type matrix metalloproteinases (MT-MMPs) and compare their expression pattern in rheumatoid **arthritis** (RA) and normal synovium. Methods: Polymerase chain reaction (PCR) with specific primers was performed to analyze the presence of MT1-, MT2-, MT3-, and MT4-MMP in synovial tissue and synovial fibroblasts from 10 patients with RA and 4 subjects without **arthritis.** In addition, in situ hybridization with digoxigenin-labeled RNA probes was used to investigate the expression pattern of MT-MMPs in the synovium of these subjects. MT-MMP-expressing cells were characterized by immunohistochem. double labeling with anti-CD68 monoclonal antibodies. Results: Reverse transcription-PCR revealed the expression of MT1-, MT2-, MT3-, and MT4-MMP mRNA in all tissues and cell cultures examined However, in situ hybridization showed considerable differences in the expression pattern of the different MT-MMPs in RA synovium. MT1- and MT3-MMP mRNA were highly expressed in both the lining and the sublining layer, with more intense staining in the lining. Immunohistochem. double labeling demonstrated the presence of mRNA for MT1-MMP in fibroblasts and macrophages, as well as in osteoclast-like cells at sites of bone resorption. Expression of MT3-MMP mRNA was seen in fibroblasts and some macrophages. Expression of MT2- and MT4-MMP was characterized by staining of only a few CD68-neg. fibroblasts, and no differences could be found between the lining and sublining. Normal synovial samples showed only limited staining for all MT-MMPs. Conclusion: the authors' results indicate a role for MT1-MMP not only in the matrix degradation by fibroblasts, but also in osteoclast-mediated bone resorption in RA. Given the ability of MT1-MMP to activate MMP-2 and **MMP-13**, the findings also point to a cooperation between fibroblasts and macrophages in degrading cartilage and bone. While MT3-MMP is also intensely expressed in RA synovium, MT2- and MT4-MMP appear not to be involved in rheumatoid joint destruction.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:487849 CAPLUS
DOCUMENT NUMBER: 133:162557
TITLE: Expression of matrix metalloproteinases and their inhibitors during hepatic tissue repair in the rat
AUTHOR(S): Knittel, Thomas; Mehde, Mirko; Grundmann, Anka; Saile, Bernhard; Scharf, Jens-Gerd; Ramadori, Giuliano
CORPORATE SOURCE: Department of Internal Medicine, Section of Gastroenterology and Endocrinology, University of Gottingen, Gottingen, 37075, Germany
SOURCE: Histochemistry and Cell Biology (2000), 113(6), 443-453
CODEN: HCBIFP; ISSN: 0948-6143
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Matrix metalloproteinases (MMPs) and their specific inhibitors (TIMPs) are thought to play an essential role in liver injury associated with tissue remodeling. However, their distinct expression profile in different liver repair models still remains to be established. Hepatic expression of collagenase (**MMP-13**), gelatinases A and B (MMP-2, -9), stromelysin-1 and -2 (MMP-3, -10), membrane-type MMP-1 (MMP-14), and TIMP-1 and -2 was studied following single and repeated CCl4-mediated injury and after partial hepatectomy. Expression was analyzed by reverse transcription-PCR (RT-PCR), northern blot anal., zymog., and immunohistochem. Following a single toxic liver injury, MMPs and TIMPs were induced in a distinct time frame in that expression of most MMPs was induced during the early phase of liver injury, was maximal during the inflammatory reaction, and was diminished in the recovery phase. In contrast, TIMP and MMP-2 steady state mRNA levels remained constant in the early phase, were strongly induced during tissue **inflammation**, and remained increased until the recovery phase. Interestingly, hepatic TNF-α expression paralleled the MMP induction profile, while the increase of TGF-β1 expression mapped to the increase of TIMPs. Chronic liver injury was accompanied by an increase in the steady state mRNA levels of MMP-2 and TIMPs, while other MMPs remained more or less unchanged or were diminished. Partial hepatectomy was followed by a dramatic increase of MMP-14 and to a lesser extent also of TIMP-1 expression; other MMPs and TIMPs were not significantly induced. Liver injury is accompanied by profound changes in hepatic MMP/TIMP expression, the latter being critically dependent on the type of injury. Single toxic injury resulting in complete restoration was characterized by a sequential induction of MMPs and TIMPs suggesting initial matrix breakdown and matrix restoration thereafter. Chronic liver injury leading to fibrosis displays overall diminished matrix degradation mainly through TIMP induction, while liver regeneration induced by partial hepatectomy caused an induction of MMP-14 and TIMP-1 only, which might be unrelated to matrix turnover but connected to pericellular fibrinolysis or fibrolysis required for hepatocellular replication.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:468813 CAPLUS
DOCUMENT NUMBER: 133:191360
TITLE: Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction
AUTHOR(S): Ducharme, Anique; Frantz, Stefan; Aikawa, Masanori; Rabkin, Elena; Lindsey, Merry; Rohde, Luis E.; Schoen, Frederick J.; Kelly, Ralph A.; Werb, Zena; Libby,

Peter; Lee, Richard T.
CORPORATE SOURCE: Cardiovascular Division, Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: Journal of Clinical Investigation (2000), 106(1), 55-62
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Matrix metalloproteinase-9 (MMP-9) is prominently overexpressed after myocardial infarction (MI). We tested the hypothesis that mice with targeted deletion of MMP9 have less left ventricular (LV) dilation after exptl. MI than do sibling wild-type (WT) mice. Animals that survived ligation of the left coronary artery underwent echocardiog. studies after MI; all analyses were performed without knowledge of mouse genotype. By day 8, MMP9 knockout (KO) mice had significantly smaller increases in end-diastolic and end-systolic ventricular dimensions at both midpapillary and apical levels, compared with infarcted WT mice; these differences persisted at 15 days after MI. MMP-9 KO mice had less collagen accumulation in the infarcted area than did WT mice, and they showed enhanced expression of MMP-2, **MMP-13**, and TIMP-1 and a reduced number of macrophages. We conclude that targeted deletion of the MMP9 gene attenuates LV dilation after exptl. MI in mice. The decrease in collagen accumulation and the enhanced expression of other MMPs suggest that MMP-9 plays a prominent role in extracellular matrix remodeling after MI.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:467699 CAPLUS
DOCUMENT NUMBER: 134:15861
TITLE: Constitutive expression and regulation of collagenase-3 in human breast **cancer** cells
AUTHOR(S): Selvamurugan, Nagarajan; Partridge, Nicola C.
CORPORATE SOURCE: Department of Pharmacological and Physiological Science, St. Louis University School of Medicine, St. Louis, MO, 63104, USA
SOURCE: Molecular Cell Biology Research Communications (2000), 3(4), 218-223
CODEN: MCBCFS; ISSN: 1522-4724
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Matrix metalloproteinases (MMPs) are a family of secreted or transmembrane proteins that have been implicated in multiple physiol. and pathol. processes related to extracellular matrix turnover. Recent evidence strongly suggests a role for collagenase-3 (**MMP-13**) in tumor metastasis and invasion. We report here that collagenase-3 is constitutively expressed in the breast **cancer** cell line MDA-MB231 (MDA) and outline the mol. mechanism regulating its expression. Functional anal. of the collagenase-3 promoter showed that both the activator protein-1 (AP-1) site and the runt domain (RD) binding site were required for maximal constitutive expression of collagenase-3 in MDA cells. Determination of factors binding to those sites by Northern anal. and transient transfections identified the requirement of Fra-1, c-Jun, and Cbfa1 for basal collagenase-3 promoter activity in MDA cells. (c) 2000 Academic Press.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

10/ 075,073

ACCESSION NUMBER: 2000:466550 CAPLUS
DOCUMENT NUMBER: 133:191783
TITLE: Interleukin-1β and tumor necrosis factor-α decrease collagen synthesis and increase matrix metalloproteinase activity in cardiac fibroblasts in vitro
AUTHOR(S): Siwik, Deborah A.; Chang, Donny L.-F.; Colucci, Wilson S.
CORPORATE SOURCE: Myocardial Biology Unit, Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston University Medical Center, Boston, MA, 02118, USA
SOURCE: Circulation Research (2000), 86(12), 1259-1265
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors tested the hypothesis that the inflammatory cytokines can regulate fibroblast extracellular matrix metabolism Neonatal and adult rat cardiac fibroblast cultures in vitro were exposed to interleukin (IL)-1β (4 ng/mL), tumor necrosis factor-α (TNF-α; 100 ng/mL), IL-6 (10 ng/mL), or interferon-γ (IFN-γ; 500 U/mL) for 24 h. IL-1β, and to a lesser extent TNF-α, decreased collagen synthesis, which was measured as collagenase-sensitive [3H]proline incorporation, but had no effect on cell number or total protein synthesis. IL-1β decreased the expression of procollagen α1(I), α2(I), and α1(III) mRNA, but increased the expression of procollagen α1(IV), α2(IV), and fibronectin mRNA, indicating a selective transcriptional downregulation of fibrillar collagen synthesis. IL-1β and TNF-α each increased total matrix metalloproteinase (MMP) activity as measured by in-gel zymog., causing specific increases in the bands corresponding to **MMP-13**, MMP-2, and MMP-9. IL-1β increased the expression of proMMP-2 and proMMP-3 mRNA, suggesting that increased metalloproteinase activity is due, at least in part, to increased transcription. The effects of IL-1β were not dependent on NO production Thus, IL-1β and TNF-α decrease collagen synthesis and activate MMPs that degrade collagen. IL-1β and TNF-α may thus contribute to ventricular dilation and myocardial failure by promoting the remodeling of interstitial collagen.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:444772 CAPLUS
DOCUMENT NUMBER: 133:333413
TITLE: Matrix metalloproteinases and tissue inhibitors of metalloproteinases in synovial fluids from patients with rheumatoid **arthritis** or osteoarthritis
AUTHOR(S): Yoshihara, Yasuo; Nakamura, Hiroyuki; Obata, Ken'ichi; Yamada, Harumoto; Hayakawa, Taro; Fujikawa, Kyosuke; Okada, Yasunori
CORPORATE SOURCE: Department of Orthopaedic Surgery, National Defence Medical College, UK
SOURCE: Annals of the Rheumatic Diseases (2000), 59(6), 455-461
CODEN: ARDIAO; ISSN: 0003-4967
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Matrix metalloproteinases (MMPs) are expressed in joint tissues of patients with rheumatoid **arthritis** (RA) and osteoarthritis (OA). The objective of this study was to define the steady state levels of 7 different MMPs and 2 tissue inhibitors of metalloproteinases (TIMPs) as

well as the potential metalloproteinase activity in the synovial fluid (SF) to provide more insight into the role of MMPs in cartilage destruction in RA and OA. Levels of MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, **MMP-13**, TIMP-1, and TIMP-2 in SF aspirated from knee joints of 97 patients with RA and 103 patients with OA were measured by the corresponding one step sandwich enzyme immunoassays. Proteolytic activity of MMPs in these SFs was examined in an assay using [3H]carboxymethylated transferrin substrate in the presence of inhibitors of Ser and Cys proteinases after activation with p-aminophenylmercuric acetate (APMA). Destruction of RA knee joints was radiog. evaluated. Levels of MMP-1, MMP-2, MMP-3, MMP-8, and MMP-9 were significantly higher in RA SF than in OA SF. MMP-7 and **MMP-13** were detectable in more than 45% of RA SFs and in less than 20% of OA SFs, resp. Among the MMPs examined, MMP-3 levels were extremely high compared with those of other MMPs. Direct correlations were seen between the levels of MMP-1 and MMP-3 and between those of MMP-8 and MMP-9 in RA SF. Although the levels of MMP-1 and MMP-3 increased even in the early stage of RA, those of MMP-8 and MMP-9 were low in the early stage and increased with the progression of RA. Molar ratios of the total amts. of the MMPs to those of the TIMPs were 5.2-fold higher in patients with RA than in OA, which was significant. APMA-activated metalloproteinase activity in SF showed a similar result, and a direct correlation was seen between the molar ratios and the activity in RA SF. These results show that high levels of MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and TIMP-1 are present in RA SF and suggest that once these MMPs are fully activated, they have an imbalance against TIMPs, which may contribute to the cartilage destruction in RA.

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:381701 CAPLUS
DOCUMENT NUMBER: 133:17487
TITLE: Preparation of tetrahydrobenzodiazepine hydroxamic acids as matrix metalloproteinase inhibitors
INVENTOR(S): Albright, Jay D.; Delos, Santos Efren G.; Du, Xuemei
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: U.S., 61 pp., Cont. of U.S. Ser. No. 237,058, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6071903	A	20000606	US 1999-318919	19990526

PRIORITY APPLN. INFO.: US 1998-93057P P 19980127
US 1999-237058 B1 19990126

OTHER SOURCE(S): MARPAT 133:17487
GI

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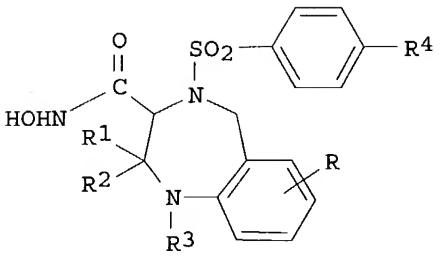


I

AB Title compds. [I; R = H, (un)substituted NH2, OH, alkyl, alkoxy, etc.; R1,R2 = H or Me; R3 = (hetero)arylcarbonyl, etc.; R4 = alkoxy, OC6H4R5-4, (un)substituted Ph, etc.; R5 = H, halo, (un)substituted heteroaryl, etc.] were prepared Thus, HOCH2CH(NH2)CO2CMe3(preparation give) was N-acylated by 4-(MeO)C6H4SO2Cl and the product N-alkylated by 2-(O2N)C6H4CH2Br to give serine derivative II (R6 = NO2, R7 = OH, R8 = H) which was reduced and the product N-acylated by 3-(F3C)C6H4COCl to give, after dehydration, II [R6 = 3-(F3C)C6H4CONH, R7R8 = bond]. The latter was cyclized to give, after saponification and amidation, I [R = R1 = R2 = H, R3 = COC6H4(CF3)-3, R4 = OMe]. Data for biol. activity of I were given.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:373564 CAPLUS

DOCUMENT NUMBER: 133:118915

TITLE: Secreted and membrane-associated matrix metalloproteinases of IL-2-activated NK cells and their inhibitors

AUTHOR(S): Kim, Myoung H.; Kitson, Richard P.; Albertsson, Per; Nannmark, Ulf; Basse, Per H.; Kuppen, Peter J. K.; Hokland, Marianne E.; Goldfarb, Ronald H.

CORPORATE SOURCE: Department of Molecular Biology and Immunology, University of North Texas Health Science Center at Fort Worth and Institute for Cancer Research, Fort Worth, TX, 76107, USA

SOURCE: Journal of Immunology (2000), 164(11), 5883-5889
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

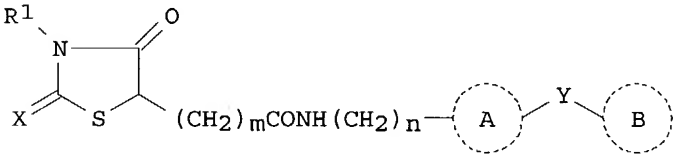
AB The authors have previously documented that rat IL-2-activated NK (A-NK) cells produce matrix metalloproteinase-2 (MMP-2) and MMP-9. In this study, the authors describe mouse A-NK cell-derived MMPs, including MT-MMPs, and also TIMPs. RT-PCR anal. from cDNA of mouse A-NK cells revealed mRNA for MMP-2, MMP-9, MMP-11, **MMP-13**, MT1-MMP, MT2-MMP, TIMP-1, and TIMP-2. MMP-2 and MMP-9 expression was confirmed by gelatin zymog. Moreover, the authors report for the first time that MT-MMPs are expressed by NK cells, i.e., large granular lymphocytes as determined by both RT-PCR and Western blots. TIMP-1 expression was detected as a 29-kDa protein in Western blots. It is intriguing that TIMP-2 protein from A-NK cells was also detected as a 29-kDa protein, which is clearly different from the previously reported mol. mass of 21 kDa in mouse and human cells. In addition, inhibition of MMPs by BB-94, a selective inhibitor of MMP, significantly inhibited the ability of mouse A-NK cells to migrate through Matrigel, a model basement membrane. Taken together, these findings suggest that A-NK cells may therefore use multiple MMPs in various cellular functions, including degradation of various extracellular matrix mols. as they extravasate from blood vessels and accumulate within **cancer** metastases following their adoptive

transfer.
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

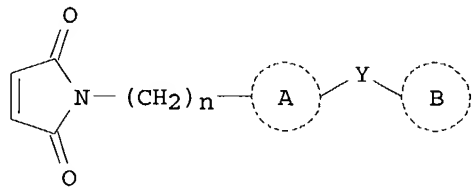
L4 ANSWER 19 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:356169 CAPLUS
DOCUMENT NUMBER: 133:4651
TITLE: Preparation of thiazolidine derivatives, matrix metalloprotease inhibitors containing them, and their therapeutic uses
INVENTOR(S): Kawamura, Noriaki; Yamashita, Toshio; Takizawa, Masayuki; Yoshimura, Koji
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 42 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000143650	A2	20000526	JP 1998-323767	19981113

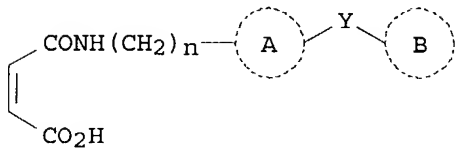
PRIORITY APPLN. INFO.: JP 1998-323767 19981113
OTHER SOURCE(S): CASREACT 133:4651; MARPAT 133:4651
GI



I



II



III

AB The derivs. I [rings A and B = (un)substituted homocyclic or heterocyclic group, wherein the substituents are bonded together with Y to form a condensed ring; R1 = H, (un)substituted hydrocarbyl; X = O, S; Y = linking group, divalent (un)substituted C1-3 aliphatic hydrocarbylene; O(CH2)p (p = 0-3), S(O)r (r = 0-2), CONH, NHCO, NHCONH, NHSO2; m = 1, 2; n = 0, 1] or their salts are prepared by treatment of R1NHC(S)CH (R1 = same as above) or their salts with maleimide derivs. II (A, B, Y, and n = same as above) or maleamic acid derivs. III (A, B, Y, and n = same as above) or their salts. Also claimed are matrix metalloproteinase inhibitors containing I or their

salts and prophylactic and therapeutic agents containing I or their salts for osteoarthritis, rheumatoid **arthritis**, osteoporosis, **cancer**, periodontal diseases, or corneal ulcer. N-[4-(4-methylphenoxy)benzyl]maleimide, prepared from 4-bromobenzonitrile, 4-methylphenol, and maleic anhydride, was treated with isobutylamine, Et3N, and CS2 to give 3-isobutyl-N-[4-(4-methylphenoxy)benzyl]-4-oxo-2-thioxo-5-thiazolidineacetamide. This inhibited human recombinant **MMP-13** at IC50 2 nM.

L4 ANSWER 20 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:326097 CAPLUS
DOCUMENT NUMBER: 133:133237
TITLE: Calcium crystal effects on the cells of the joint. Implications for pathogenesis of disease
AUTHOR(S): Cheung, Herman S.
CORPORATE SOURCE: Research Service and Geriatric Research Education and Clinical Center, Miami Veterans Affairs Medical Center and Division of Rheumatology and Immunology, University of Miami School of Medicine, Miami, FL, USA
SOURCE: Current Opinion in Rheumatology (2000), 12(3), 223-227
CODEN: CORHES; ISSN: 1040-8711
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review is given with 32 refs. In the past 3 yr, there was considerable progress in delineating the mechanism of Ca-containing crystal-induced cell activation: (1) the identification of Ca2+ influx and p42/44 mitogen-activated protein kinase activation as the signal transduction pathways; (2) induction of nuclear transcription factors of cyclic adenosine monophosphate (cAMP) response element binding protein, activator protein-1, and nuclear factor κB; (3) the differential role of crystal endocytosis and dissoln. in crystal-induced metalloproteinase synthesis and mitogenesis; (4) crystal upregulation of matrix metalloproteinases, including **MMP-13** but down regulation of tissue inhibitor of metalloproteinase-1 and -2, thus magnifying the degenerative effect of crystals. Phosphocitrate, a specific inhibitor of biol. effect of Ca crystals, reverses the degenerative effects of crystals.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:318724 CAPLUS
DOCUMENT NUMBER: 133:146750
TITLE: Hydrolysis of triple-helical collagen peptide models by matrix metalloproteinases
AUTHOR(S): Lauer-Fields, Janelle L.; Tuzinski, Kathleen A.; Shimokawa, Ken-Ichi; Nagase, Hideaki; Fields, Gregg B.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Florida Atlantic University, Boca Raton, FL, 33431-0991, USA
SOURCE: Journal of Biological Chemistry (2000), 275(18), 13282-13290
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The matrix metalloproteinase (MMP) family has been implicated in the process of a variety of diseases such as **arthritis**, atherosclerosis, and tumor cell metastasis. To study the mechanisms of MMP action on collagenous substrates, we have constructed homotrimeric triple-helical peptide (THP) models of the collagenase cleavage sites in types I and II collagen. The THPs incorporate either the

α1(I)772-786 or the α1(II)772-783 sequence. The α1(I)772-786 and α1(II)772-783 THPs were hydrolyzed by MMP-1 at the Gly-Ile and Gly-Leu bonds, resp., analogous to the bonds cleaved in corresponding native collagens. Thus, the THPs contained all necessary information to direct MMP-1 binding and proteolysis. Subsequent investigations using the α1(I)772-786 THP showed hydrolysis by MMP-2, **MMP-13**, and a COOH-terminal domain-deleted MMP-1 (MMP-1(Δ243-450)) but not by MMP-3 or a COOH-terminal domain-deleted MMP-3 (MMP-3(Δ248-460)). Kinetic analyses showed a kcat/Km value of 1,808 s-1 M-1 for MMP-1 hydrolysis of α1(I)772-786 THP, approx. 10-fold lower than for type I collagen. The effect is caused primarily by relative Km values. MMP-2 and **MMP-13** cleaved the THP more rapidly than MMP-1, but MMP-2 cleavage occurred at distinct multiple sites. Comparison of MMP-1 and MMP-1(Δ243-450) hydrolysis of α1(I)772-786 THP showed that both can cleave a triple-helical substrate with a slightly higher Km value for MMP-1(Δ243-450). We propose that the COOH-terminal domain of MMPs is necessary for orienting whole, native collagen mols. but may not be necessary for binding to and cleaving a THP. This proposal is consistent with the large distance between the MMP-1 catalytic and COOH-terminal domains observed by three-dimensional structural anal. and supports previous suggestions that the features of the catalytic domain contribute significantly toward enzyme specificity.

REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:255903 CAPLUS
DOCUMENT NUMBER: 133:56951
TITLE: Evolution of matrix metalloprotease and tissue inhibitor expression during **heart** failure progression in the infarcted rat
AUTHOR(S): Peterson, J. T.; Li, H.; Dillon, L.; Bryant, J. W.
CORPORATE SOURCE: Division of Warner-Lambert Company, Parke-Davis Pharmaceutical Research, Department of Cardiovascular Therapeutics, Ann Arbor, MI, USA
SOURCE: Cardiovascular Research (2000), 46(2), 307-315
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: Characterize the time course of matrix metalloproteinase (MMP-1, -2, -3, -7, -9, -11, -12, -13, and -14) and endogenous tissue inhibitors of MMPs (TIMP-1, -2, -3, and -4) upregulation during left ventricular (LV) remodeling following myocardial infarction (MI) in rats. Methods: The descending left coronary artery of male rats (Rattus norvegicus) was ligated to produce a MI. LV function and dilation were assessed from 1 day to 16 wk post-MI. Protein and mRNA extraction was done on LV samples containing scar and myocardium together. Gelatinase activity was measured by zymog. Westerns were run on the MMPs known to cleave fibrillar collagen in the rat (MMP-8, -13, and -14) as well as TIMP-1, -2, and -4. Results: Average infarct size was 38.6%, and produced LV dysfunction and progressive LV dilation. Thoracic ascites, a marker of congestive **heart** failure (HF), was not present until 12 wk post-MI. Upregulation of MMP-2, -8, -9, -13, and -14 and TIMP-1 and TIMP-2 was detected at different time points during HF progression. Increased MMP protein levels occurred sometimes without a corresponding elevation in mRNA levels, and increased TIMP mRNA levels without increased protein levels. **MMP-13** active form was elevated during the first 2 wk post-MI while TIMP-1 and TIMP-2 protein levels were not significantly elevated until 2 wk post-MI. MMP-8 and MMP-14 protein levels increased later during **heart** failure progression. Conclusion: MMP/TIMP upregulation evolves over time following infarction

in the rat LV. Some MMPs were significantly elevated during the first week post-MI (**MMP-13**, -2, and -9) and another was not until 16 wk post-MI (MMP-14). The dissociation between LV MMP/TIMP mRNA and protein levels shows that post-translation processing occurs in the rat **heart.**

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:255902 CAPLUS
DOCUMENT NUMBER: 133:68679
TITLE: MMP/TIMP expression in spontaneously hypertensive **heart** failure rats: the effect of ACE- and MMP-inhibition
AUTHOR(S): Li, H.; Simon, H.; Bocan, T. M. A.; Peterson, J. T.
CORPORATE SOURCE: Division of Warner-Lambert Company, Parke-Davis Pharmaceutical Research, Department of Cardiovascular Therapeutics, Ann Arbor, MI, USA
SOURCE: Cardiovascular Research (2000), 46(2), 298-306
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: Determine the effect of a matrix metalloproteinase inhibitor (MMPi) and angiotensin converting enzyme inhibitor (ACEi) on collagen, MMP, tissue inhibitors of MMPs (TIMPs) expression in the spontaneously hypertensive **heart** failure (SHHF) rat. Methods: Six groups were tested: normotensive 9- and 13-mo-old Wistar-Furth (WF) rats, 9-mo-old SHHFs (compensatory hypertrophy), 13-mo-old SHHFs with HF, and 13-mo-old SHHFs orally administered with either an MMPi (PD166793, 5 mg kg-1 day-1) or ACEi (quinapril, 10 mg kg-1 day-1) for 4 mo. Collagen volume fraction was assessed histomorphometrically. Left ventricular (LV) mRNA [MMP-1,-2,-3,-7,-9,-11,-13,-14; TIMP-1,-2,-3,-4; and collagen α1(I) and α1(III)] and protein (MMP-2 and MMP-9 zymog. activity; Western blot anal. of **MMP-13**, and TIMP-1,-2,-4) levels could be quantified. Results: Collagen mRNA levels were elevated in SHHFs compared to age-matched controls, but collagen volume fraction was elevated only in 13-mo-old SHHFs (.apprx.2+). Only MMP-2 mRNA levels increased significantly with HF. However, MMP-2 and MMP-9 zymog. activity, and **MMP-13** protein levels increased. TIMP-1 and TIMP-2 mRNA and protein levels increased, and TIMP-4 protein levels decreased in SHHFs vs. controls. Both drug treatments reduced LV dilation; preserved systolic function; and normalized MMP/TIMP expression. Both drug treatments also reduced collagen volume fraction, but only quinapril reduced collagen mRNA levels and LV hypertrophy. Conclusions: The divergent effect of MMPi and ACEi on collagen mRNA levels and hypertrophy indicate that drug efficacy is mediated by different pathways in the SHHF rat.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:235651 CAPLUS
DOCUMENT NUMBER: 133:148659
TITLE: Selective enhancement of collagenase-mediated cleavage of resident type II collagen in cultured osteoarthritic cartilage and arrest with a synthetic inhibitor that spares collagenase 1 (matrix metalloproteinase 1)
AUTHOR(S): Dahlberg, Leif; Billinghurst, R. Clark; Manner, Paul; Nelson, Fred; Webb, Ginette; Ionescu, Mirela; Reiner, Agnes; Tanzer, Michael; Zukor, David; Chen, Jeffrey; Van Wart, Harold E.; Poole, A. Robin

10/ 075,073

CORPORATE SOURCE: University Hospital, Malmo, Swed.
SOURCE: Arthritis & Rheumatism (2000), 43(3), 673-682
CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of this study was to examine whether type II collagen cleavage by collagenase and loss of proteoglycan are excessive in human osteoarthritic (OA) articular cartilage compared with nonarthritic articular cartilage, and whether this can be inhibited by a selective synthetic inhibitor that spares collagenase 1 (matrix metalloproteinase 1 [MMP-1]). Articular cartilage samples were obtained during surgery from 11 patients with OA and at autopsy from 5 adults without **arthritis**. The articular cartilage samples were cultured in serum-free medium. A collagenase-generated neoepitope, which reflects cleavage of type II collagen, and proteoglycan glycosaminoglycan (GAG), which predominantly reflects aggrecan release, were assayed in culture media. In addition, cultures were performed using either of 2 synthetic MMP inhibitors, both of which inhibited collagenase 2 (MMP-8) and collagenase 3 (**MMP-13**), but one of which spared collagenase 1. Cultures were also biolabeled with 3H-proline in the presence and absence of these inhibitors to measure collagen synthesis (as tritiated hydroxyproline) and incorporation in articular cartilage. As a group, cleavage of type II collagen by collagenase was significantly increased in OA cartilage samples. In contrast, proteoglycan (GAG) release was not increased. This release of a collagenase-generated epitope was inhibited by both MMP inhibitors in 2 of 5 nonarthritic samples and in 9 of 11 OA cartilage samples. The inhibitor that spared collagenase 1 was generally more effective and inhibited release from 4 of 5 nonarthritic cartilage samples and the same OA cartilage samples. Group analyses revealed that the inhibition of collagenase neoepitope release by both inhibitors was significant in the OA patient cartilage, but not in the nonarthritic cartilage. Proteoglycan loss was unaffected by either inhibitor. Newly synthesized collagen (predominantly, type II) exhibited increased incorporation in OA cartilage, but only in the presence of the inhibitor that arrested collagenase 1 activity. These results further indicate that the digestion of type II collagen by collagenase is selectively increased in OA cartilage, and that this can be inhibited in the majority of cases by a synthetic inhibitor that can inhibit collagenases 2 and 3, but not collagenase 1. The results also suggest that in OA, newly synthesized collagen is digested, but in a different manner than that of resident mols. Proteoglycan release was not increased in OA cartilage and was unaffected by these inhibitors. Inhibitors of this kind may be of value in preventing damage to type II collagen in human arthritic articular cartilage,.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:235650 CAPLUS
DOCUMENT NUMBER: 133:149020
TITLE: Comparison of the degradation of type II collagen and proteoglycan in nasal and articular cartilages induced by interleukin-1 and the selective inhibition of type II collagen cleavage by collagenase
AUTHOR(S): Billinghurst, R. Clark; Wu, William; Ionescu, Mirela; Reiner, Agnes; Dahlberg, Leif; Chen, Jeffrey; Van Wart, Harold; Poole, A. Robin
CORPORATE SOURCE: Colorado State University, Fort Collins, CO, USA
SOURCE: Arthritis & Rheumatism (2000), 43(3), 664-672
CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal

10/ 075,073

LANGUAGE: English

AB Interleukin-1α (IL-1α)-induced degradation of nasal and articular cartilages was compared in terms of proteoglycan loss and type II collagen cleavage, denaturation, and release; the temporal relationship of these changes was examined; and the effects of an inhibitor of collagenase 2 and collagenase 3 on these catabolic processes were investigated. Disks of mature bovine nasal and articular cartilages were cultured with or without human IL-1α (5 ng/mL) with or without RS102,481, a selective synthetic inhibitor of collagenase 2 and collagenase 3 (matrix metalloproteinase 8 [MMP-8] and **MMP-13**, resp.) but not of collagenase 1 (MMP-1). Immunoassays were used to measure collagenase-generated type II collagen cleavage neoepitope (antibody COL2-3/4Cshort) and denaturation (antibody COL2-3/4m), as well as total type II collagen content (antibody COL2-3/4m) in articular cartilage and culture media. A colorimetric assay was used to measure total proteoglycan concentration (principally of aggrecan) as sulfated glycosaminoglycans (sGAG). IL-1α initially induced a decrease in tissue proteoglycan content in nasal cartilage. A progressive loss of proteoglycan was noted during culture in articular cartilages, irresp. of the presence of IL-1α. In both cartilages, proteoglycan loss was followed by IL-1α-induced cleavage of type II collagen by collagenase, which was often reflected by increased denaturation. The inhibitor RS102,481 had no clear effect on the reduction in proteoglycan content (measured by sGAG) and collagen denaturation in either cartilage, but at 10 nM it inhibited the enhanced cleavage of type II collagen, partially in nasal cartilage and completely in articular cartilage. IL-1α-induced cleavage and denaturation of type II collagen is observed in both hyaline cartilages and is secondary to proteoglycan loss. It probably involves different collagenases, since there is no evidence of a rate-limiting role for collagenase 1 in articular cartilage, unlike the case for nasal cartilage. Inhibitors of this kind may be of value in the treatment of cartilage damage in **arthritis**. Also, the ability to detect the release of type II collagen collagenase-generated fragments from degraded cartilage offers the potential to monitor cartilage collagen damage and its control in vivo.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:231563 CAPLUS

DOCUMENT NUMBER: 133:118279

TITLE: Upregulation of gelatinases A and B, collagenases 1 and 2, and increased parenchymal cell death in COPD

AUTHOR(S): Segura-Valdez, Lourdes; Pardo, Annie; Gaxiola, Miguel; Uhal, Bruce D.; Becerril, Carina; Selman, Moises

CORPORATE SOURCE: Instituto Nacional de Enfermedades Respiratorias, Mexico City, 14080, Mex.

SOURCE: Chest (2000), 117(3), 684-694
CODEN: CHETBF; ISSN: 0012-3692

PUBLISHER: American College of Chest Physicians

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: A central feature in the pathogenesis of COPD is the **inflammation** coexisting with an abnormal protease/antiprotease balance. However, the possible role of different serine and metalloproteinases remains controversial. Patients and measurements: We examined the expression of gelatinases A and B (matrix metalloproteinase [MMP]-2 and MMP-9); collagenases 1, 2, and 3 (MMP-1, MMP-8, and **MMP-13**); as well as the presence of apoptosis in lung tissues of 10 COPD patients and 5 control subjects. In addition, gelatinase-A and gelatinase-B activities were assessed in BAL obtained from eight COPD patients, and from six healthy nonsmokers and six healthy smoker control subjects. Setting: Tertiary referral center and university

labs. of biochem., and lung cell kinetics. Results: Immunohistochem. anal. of COPD lungs showed a markedly increased expression of collagenases 1 and 2, and gelatinases A and B, while collagenase 3 was not found. Neutrophils exhibited a pos. signal for collagenase 2 and gelatinase B, whereas collagenase 1 and gelatinase A were revealed mainly in macrophages and epithelial cells. BAL gelatin zymog. showed a moderate increase of progelatinase-A activity and intense bands corresponding to progelatinase B. In situ end labeling of fragmented DNA displayed foci of pos. endothelial cells, although some alveolar epithelial, interstitial, and inflammatory cells also revealed intranuclear staining. Conclusion: These findings suggest that there is an upregulation of collagenase 1 and 2 and gelatinases A and B, and an increase in endothelial and epithelial cell death, which may contribute to the pathogenesis of COPD through the remodeling of airways and alveolar structures.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:172706 CAPLUS
DOCUMENT NUMBER: 133:40112
TITLE: Immunochemical characterization of assay for carboxyterminal telopeptide of human type I collagen: loss of antigenicity by treatment with cathepsin K
AUTHOR(S): Sassi, M.-L.; Eriksen, H.; Risteli, L.; Niemi, S.; Mansell, J.; Gowen, M.; Risteli, J.
CORPORATE SOURCE: Department of Clinical Chemistry, University of Oulu, Oulu, Finland
SOURCE: Bone (New York) (2000), 26(4), 367-373
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The assay for the cross-linked carboxyterminal telopeptide of type I collagen (ICTP) has been shown to reflect increased type I collagen degradation in such pathol. conditions as bone metastases and rheumatoid **arthritis**, but to be rather insensitive to the changes in physiol. bone collagen turnover (e.g., induced by estrogen or bisphosphonate treatment). To determine the reasons for this discrepancy we localized the antigenic determinant recognized by the ICTP assay and studied the effects of two major osteoclastic proteinases, cathepsin K (EC 3.4.22.38) and matrix metalloproteinase-9 (MMP-9; gelatinase B; EC 3.4.24.35), on immunoreactivity. The antigenic determinant was shown to reside within the hydrophobic phenylalanine-rich regions of the carboxyterminal telopeptides of the two α1 chains of human type I collagen, situated between the triple helical domain and the lysine-derived trivalent cross-link. This conclusion was based on differences between the amino acid sequences and cross reactivities of the corresponding human and bovine antigens before and after proteolytic treatments with chymotrypsin. A trivalent cross-link is necessary for providing such a structure, because the divalently cross-linked and monomeric natural and synthetic peptides from the same region, but containing only one phenylalanine-rich sequence, showed poor immunoreaction. Recombinant human cathepsin K cleaved the trivalently cross-linked ICTP structure at two sites between the phenylalanine-rich region and the cross-link, destroying the reactivity with ICTP antibodies. On the contrary, the treatment of isolated ICTP by the matrix metalloproteinases MMP-9 (gelatinase B), MMP-1 (collagenase 1), or **MMP-13** (collagenase 3) had no effect on the immunoreaction. Our results indicate that the increased circulating concns. of ICTP found in several clin. situations are most likely produced by matrix metalloproteinases, whereas cathepsin K-mediated, osteoclastic bone resorption destroys ICTP antigenicity.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:168136 CAPLUS
DOCUMENT NUMBER: 132:217151
TITLE: Fluorinated butyric acids and their derivatives as inhibitors of matrix metalloproteinases, their preparation, and pharmaceutical compositions containing them
INVENTOR(S): Roth, Bruce David; O'Brien, Patrick Michael; Sliskovic, Drago Robert
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: U.S., 18 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6037361	A	20000314	US 1998-36751	19980309

PRIORITY APPLN. INFO.: US 1998-36751 19980309
OTHER SOURCE(S): MARPAT 132:217151
AB Fluorinated butyric acids and derivs., methods for their preparation, and pharmaceutical compns. containing them are described which are useful as inhibitors of matrix metalloproteinases, particularly gelatinase A (72 kD gelatinase) and stromelysin-1, and also collagenase, matrilysin, and **MMP-13**, and for the treatment of multiple sclerosis, atherosclerotic plaque rupture, aortic aneurism, **heart** failure, restenosis, periodontal disease, corneal ulceration, burns, decubital ulcers, wound healing, **cancer**, **inflammation**, pain, **arthritis**, or other autoimmune or inflammatory disorders dependent on tissue invasion by leukocytes or other activated migrating cells, acute and chronic neurodegenerative disorders including stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, AIDS, Parkinson's disease, Huntington's disease, prion diseases, myasthenia gravis, and Duchenne's muscular dystrophy. Preparation of e.g. 4-dibenzofuran-2-yl-3,3-difluoro-4-oxobutyric acid is described.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:160200 CAPLUS
DOCUMENT NUMBER: 132:291966
TITLE: Candidate genes for the hypoxic tumor phenotype
AUTHOR(S): Koong, Albert C.; Denko, Nicholas C.; Hudson, Karen M.; Schindler, Cornelia; Swiersz, Lillian; Koch, Cameron; Evans, Sydney; Ibrahim, Hani; Le, Quynh T.; Terris, David J.; Giaccia, Amato J.
CORPORATE SOURCE: Departments of Radiation Oncology, Stanford University School of Medicine, Stanford, CA, 94305-5468, USA
SOURCE: Cancer Research (2000), 60(4), 883-887
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, the authors have analyzed changes induced by hypoxia at the transcriptional level of genes that could be responsible for a more aggressive phenotype. Using a series of DNA array membranes, the authors identified a group of hypoxia-induced genes that included plasminogen activator inhibitor-1 (PAI-1), insulin-like growth factor-binding protein 3 (IGFBP-3), endothelin-2, low-d. lipoprotein receptor-related protein

(LRP), BCL2-interacting killer (BIK), migration-inhibitory factor (MIF), matrix metalloproteinase-13 (**MMP-13**), fibroblast growth factor-3 (FGF-3), GADD45, and vascular endothelial growth factor (VEGF). The induction of each gene was confirmed by Northern blot anal. in two different squamous cell carcinoma-derived cell lines. The authors also analyzed the kinetics of PAI-1 induction by hypoxia in more detail because it is a secreted protein that may serve as a useful mol. marker of hypoxia. On exposure to hypoxia, there was a gradual increase in PAI-1 mRNA between 2 and 24 h of hypoxia followed by a rapid decay after 2 h of reoxygenation. PAI-1 levels were also measured in the serum of a small group of head and neck **cancer** patients and were found to correlate with the degree of tumor hypoxia found in these patients.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 30 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:152881 CAPLUS
DOCUMENT NUMBER: 132:277416
TITLE: Differential expression of matrix metalloproteinases and their inhibitors in non-small cell lung **cancer**
AUTHOR(S): Thomas, Pascal; Khokha, Rama; Shepherd, Frances A.; Feld, Ronald; Tsao, Ming-Sound
CORPORATE SOURCE: Service d'Oncologie Respiratoire, Hopital Ste-Marguerite, Marseille, 1 3009, Fr.
SOURCE: Journal of Pathology (2000), 190(2), 150-156
CODEN: JPTLAS; ISSN: 0022-3417
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In a comprehensive immunohistochem. study of the expression of 10 metalloproteinases (MMPs) and their 4 inhibitors (TIMPs) in 115 non-small cell lung carcinomas (NSCLCs), the findings were correlated with the histol. and clin. features of the tumors. All MMPs and TIMPs were expressed in tumors, with frequencies ranging from 41% for MMP-2 to 68% for **MMP-13**. Stromal immunoreactivity ranged from 6% for TIMP-4 to 87% for **MMP-13**. In some tumors, an overexpression of these proteins, as revealed by stronger staining in **cancer** cells than in adjacent normal bronchial epithelium, was also observed The frequency ranged from 1% for MMP-3 to 28% for **MMP -13**. Compared with squamous cell carcinoma (SqCC), adenocarcinoma (AdC) more frequently overexpressed MMP-1, -11, -13, -14, and TIMP-2, and TIMP-1 and/or TIMP-2 overexpression pos. correlated with more advanced stage disease. 0 Of the MMP or TIMP expression correlated with the ras genotype of the tumors. The higher frequency of MMP overexpression in AdC than in SqCC may relate to the greater tendency of the former for systemic metastasis. The association of TIMP-1 overexpression with more advanced disease may suggest a role in prognosis.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:100167 CAPLUS
DOCUMENT NUMBER: 132:235182
TITLE: Inhibition of collagenase-3 (**MMP-13**) expression in transformed human keratinocytes by interferon-γ is associated with activation of extracellular signal-regulated kinase-1,2 and STAT1
AUTHOR(S): Ala-Aho, Risto; Johansson, Nina; Grenman, Reidar; Fusenig, Norbert E.; Lopez-Otin, Carlos; Kahari, Veli-Matti
CORPORATE SOURCE: MediCity Research Laboratory and Department of Medical Biochemistry, University of Turku, Turku, FIN-20520,

10/ 075,073

Finland
SOURCE: Oncogene (2000), 19(2), 248-257
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Collagenase-3 (**MMP-13**) is characterized by an exceptionally wide substrate specificity and restricted expression. **MMP-13** is specifically expressed by transformed human keratinocytes in squamous cell carcinomas in vivo and its expression correlates with their invasion capacity. Here, we show, that interferon-γ (IFN-γ) markedly inhibits expression of **MMP-13** by human cutaneous SCC cells (UT-SCC-7) and by ras-transformed human epidermal keratinocytes (A-5 cells) at the transcriptional level. In addition, IFN-γ inhibits collagenase-1 (MMP-1) expression in these cells. IFN-γ abolished the enhancement of **MMP-13** and MMP-1 expression by transforming growth factor-β (TGF-β) and tumor necrosis factor-α (TNF-α), and inhibited invasion of A-5 cells through type 1 collagen. IFN-γ also rapidly and transiently activates extracellular signal-regulated kinase 1,2 (ERK1,2) and blocking ERK1,2 pathway (Raf/MEK1,2/ERK1,2) by specific MEK1,2 inhibitor PD98059 partially (by 50%) prevents Ser-727 phosphorylation of STAT1 and suppression of **MMP-13** expression by IFN-γ. Furthermore, Ser-727 phosphorylation of STAT1 by ERK1,2, or independently of ERK1,2 activation is associated with marked reduction in **MMP-13** expression. These observations identify a novel role for IFN-γ as a potent inhibitor of collagenolytic activity and invasion of transformed squamous epithelial cells, and show that inhibition of **MMP-13** expression by IFN-γ involves activation of ERK1,2 and STAT1.
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:809143 CAPLUS
DOCUMENT NUMBER: 133:15645
TITLE: Analysis of 16 different matrix metalloproteinases (MMP-1 to MMP-20) in the synovial membrane: different profiles in trauma and rheumatoid **arthritis**
AUTHOR(S): Konttinen, Yrjo; Ainola, Mia; Valleala, Heikki; Ma, Jian; Ida, Hideo; Mandelin, Jami; Kinne, Raimund W.; Santavirta, Seppo; Sorsa, Timo; Lopez-Otin, Carlos; Takagi, Michiaki
CORPORATE SOURCE: Department of Oral Medicine, University of Helsinki, Finland, FIN-00014, Finland
SOURCE: Annals of the Rheumatic Diseases (1999), 58(11), 691-697
CODEN: ARDIAO; ISSN: 0003-4967
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective-To define the pattern of mRNA expression of all human matrix metallo-proteinases (MMPs) described to date in rheumatoid **arthritis** (RA) and traumatic synovial membrane, in order to differentiate between a physiol. tissue remodelling pattern and that associated with inflammatory tissue destruction. Methods-Anal. of SwissProt protein and EMBL/GenBank nucleotide sequence banks, protein sequence alignment, reverse transcriptase-polymerase chain reaction and nucleotide sequencing were used. Results-MMP-2 (gelatinase A), MMP-3 (stromelysin-1), MMP-11 (stromelysin-3) and MMP-19 were constitutively expressed. MMP-1 (fibroblast type collagenase), MMP-9 (gelatinase B) and MMP-14 (MT1-MMP) were expressed in all RA, but only in 55-80% of trauma samples. **MMP-13** (collagenase-3) and MMP-15 (MT2-MMP)

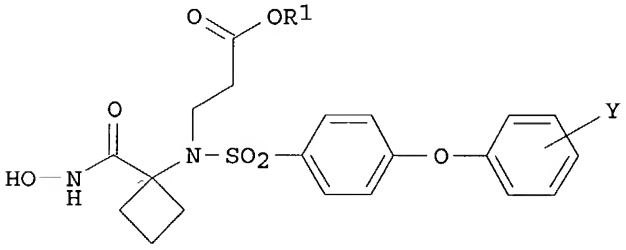
were expressed exclusively in RA (80-90% of the samples). MMP-20 (enamelysin) was absent and MMP-8 (collagenase-2) was rarely found in RA or trauma. All other MMPs (-7, -10, -12, -16, -17) had an intermediate pattern of expression. Conclusions-Some MMPs without interstitial collagenase activity seem to have a constitutive pattern of expression and probably participate in physiol. synovial tissue remodelling. Some MMPs are exclusively associated to RA synovitis, for example, **MMP-13**, which preferentially degrades type II collagen and aggrecan, and MMP-15, which activates proMMP-2 and proMMP-13 and is involved in tumor necrosis factor α processing. This clear cut rheumatoid/inflammatory MMP profile, more complex than has been previously appreciated, may facilitate inflammatory tissue destruction in RA.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:751407 CAPLUS
DOCUMENT NUMBER: 132:3251
TITLE: Preparation of 1-[N-(p-phenoxyphenylsulfonyl)-N-(2-carboxyethyl)amino]cyclobutane-1-carbohydroxamic acid derivative as matrix metalloproteinase inhibitors
INVENTOR(S): Reiter, Lawrence Alan
PATENT ASSIGNEE(S): Pfizer Products Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 17 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11322705	A2	19991124	JP 1999-102486	19990409
EP 952148	A1	19991027	EP 1999-302282	19990325
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2268484	AA	19991010	CA 1999-2268484	19990408
BR 9901250	A	20000516	BR 1999-1250	19990409
US 6156798	A	20001205	US 1999-290023	19990409

PRIORITY APPLN. INFO.: US 1998-81392P P 19980410
OTHER SOURCE(S): MARPAT 132:3251
GI



I

AB The title compds. (I; R1 = H, C1-6 alkyl; Y = H, F, Cl, CF3, C1-6 alkoxy, CF3O, difluoromethoxy, C1-6 alkyl) or pharmacol. acceptable salts are prepared These compds. as useful for the treatment of a wide range of diseases including **arthritis** (**arthritis** deformans and rheumatoid **arthritis**), inflammatory bowel diseases, Crohn's

disease, pneumatosis, chronic obstructive lung disease, Alzheimer's disease, transplanted organ toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, **cancer**, tissue ulcer, reinfarction, pericementosis (periodontal disease), epidermal hydroa, osteoporosis, loosening of transplanted artificial joint, atherosclerosis (atheroscrelotic macula rupture), aortic aneurysm (abdominal and brain aneurysm), ischemic **heart** failure, myocardial infarction, seizure, cerebral ischemia, head trauma, spinal injury, acute or chronic nerve degeneration, autoimmune diseases, Huntington's chorea (disease), migraine, depression, peripheral nerve disorders, pain, cerebral amyloid vascular disorders, amyotrophic lateral sclerosis (Charcto's disease), multiple sclerosis, contact lens vascularization (angioplasty), yellow spot degeneration, unusual wound, scald, diabetes, tumor infiltration, tumor growth, tumor metastasis, cornea scar, leutitis (sic), AIDS, septemia, and septic shock or as neutropic or cognition enhancers. Thus, 1-[N-[2-(ethoxycarbonyl)ethyl]-N-[4-(4-fluorophenoxy)phenylsulfonyl]amino] cyclobutane-1-carboxylic acid was stirred with BOP and diisopropylethylamine in DMF at room temperature for .apprx.3 h and then with O-benzylhydroxylamine hydrochloride in the presence of diisopropylethylamine at room temperature overnight followed by hydrogenolysis over 5% Pd-C in ethanol/EtOAc at room temperature and hydrogen pressure 40 psi and saponification with LiOH hydrate in ethanol and acidification with aqueous HCl to give I (R1 = H, Y = 4-F) (II). II showed IC50 of 90 and 0.6 nM against human collagenase (MMP-1) and **MMP-13**, resp.

L4 ANSWER 34 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:734063 CAPLUS
DOCUMENT NUMBER: 131:332923
TITLE: In vivo modulation of the transcription factor AP-1 by glucocorticoids
AUTHOR(S): Tuckermann, Jan Peter Gottfried
CORPORATE SOURCE: Inst. Genetik, Forschungszentrum Karlsruhe G.m.b.H., Karlsruhe, D-76021, Germany
SOURCE: Wissenschaftliche Berichte - Forschungszentrum Karlsruhe (1999), FZKA 6342, 1-136
CODEN: WBFKF5; ISSN: 0947-8620
DOCUMENT TYPE: Report
LANGUAGE: German

AB Glucocorticoids exert their various effects by alterations of gene expression. Upon binding to the glucocorticoid receptor (GR) the transcription of glucocorticoid dependent genes is regulated by 2 different mol. mechanisms. 1St, the GR mols. dimerize and bind to palindromic DNA sequences (glucocorticoid responsive elements, GRE) in the promoters of glucocorticoid regulated genes. 2Nd, the monomeric GR mol. influences the transcriptional activity of other transcription factors such as AP-1 or NFκB by protein/protein interactions without binding to DNA. So far only data from tissue culture work exist concerning the modulation of the transcriptional activity of AP-1 composed of the subunits c-Jun and c-Fos by the GR. In the present study the author showed, for the 1st time, that repression of AP-1 by glucocorticoids exist in vivo and occurs independently from the DNA binding function of the GR. AP-1/GR interactions were investigated by analyzing the expression of the interstitial collagenase gene of the mouse (collagenase-3, **MMP-13**) and addnl. AP-1 dependent genes in bone and skin. During this anal. the expression of collagenase-3 could be established as a new marker gene for the terminal differentiation stage of hypertrophic chondrocytes and osteoblasts. In osseous tissues the author demonstrated the induction of collagenase-3 by the bone resorbing parathyroid hormone (PTH). This induction was repressed in the presence of glucocorticoids as well in primary osteoblasts as in the calvarial bone of PTH and glucocorticoid treated animals. In skin the topical application with the tumor promoter TPA lead to a strong activation of the AP-1 target genes collagenase-3 and stromelysin-1 within time periods that were comparable with tissue culture

expts. The complete repression of TPA mediated expression of these genes by glucocorticoids strongly suggest that AP-1/GR interactions are the mol. basis of the anti-tumorigenic effects by glucocorticoids. To discriminate between the DNA binding dependent transactivation function and the DNA binding independent transrepression function of the GR in vivo, the author investigated the expression of AP-1 dependent genes in GRdim mice. These mice carry in their germ line a point mutation in the GR gene that leads to dimerization deficient protein which fails to bind DNA upon ligand activation. As well in embryonic fibroblasts, that the author established from these mice, as in the skin of GRdim mice no upregulation of GRE regulated genes was detectable. In contrast the transrepression function of the GR was completely preserved in cells and in the skin of GRdim mice. These results are the 1st evidence that the transrepression of AP-1 dependent genes in vivo by glucocorticoids relies on protein/protein interactions between AP-1 and GR, whereas DNA binding of the GR is not required. The anal. of the GRdim mice made it possible to use these animals to investigate, whether particular effects of glucocorticoids are based on protein/protein interactions of the GR, or whether DNA binding of the receptor is required for glucocorticoid action. By the demonstration of the repression of **inflammation** by dexamethasone in GRdim mice the author showed, for the 1st time, that the repression function of the GR is sufficient for the anti-inflammatory activity of glucocorticoids.

REFERENCE COUNT: 216 THERE ARE 216 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 35 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:700586 CAPLUS
DOCUMENT NUMBER: 132:22018
TITLE: Interleukin-6 increases rat metalloproteinase-13 gene expression through stimulation of activator protein 1 transcription factor in cultured fibroblasts
AUTHOR(S): Solis-Herruzo, Jose A.; Rippe, Richard A.; Schrum, Laura W.; De la Torre, Paz; Garcia, Inmaculada; Jeffrey, John J.; Munoz-Yague, Teresa; Brenner, David A.
CORPORATE SOURCE: Department of Medicine, University of North Carolina at Chapel Hill, NC, 27599, USA
SOURCE: Journal of Biological Chemistry (1999), 274(43), 30919-30926
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of IL-6 in collagen production and tissue remodeling is controversial. In Rat-1 fibroblasts, the authors measured the effect of IL-6 on matrix metalloproteinase-13 (**MMP-13**), c-jun, junB, and c-fos gene expression, binding of activator protein 1 (AP1) to DNA, amount of AP1 proteins, immunoreactive **MMP-13** and TIMP-1 proteins, and Jun N-terminal kinase activity. They show that IL-6 increased **MMP-13**-mRNA and **MMP-13** protein. These effects were exerted by acting on the AP1-binding site of the **MMP-13** promoter, as shown by transfecting cells with reporter plasmids containing mutations in this element. Mobility shift assays demonstrated that IL-6 induced the DNA binding activity of AP1. This effect was accompanied by a marked increase in c-Jun, JunB, and c-Fos mRNA, as well as in c-Jun protein and its phosphorylated form. The latter is not due to increased Jun N-terminal kinase activity but to a decreased serine/threonine phosphatase activity. Thus, IL-6 increases interstitial **MMP-13** gene expression at the promoter level. This effect seems to be mediated by the induction of c-jun, junB, and c-fos gene expression, by the binding of AP1 to DNA, by increasing

phosphorylated c-Jun, and by the inhibition of serine/threonine phosphatase activity. These effects of IL-6 might contribute to remodeling connective tissue.
REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 36 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:650846 CAPLUS
DOCUMENT NUMBER: 132:209
TITLE: Collagenase-3 (**MMP-13**) and its activators in rheumatoid **arthritis**: localization in the pannus-hard tissue junction and inhibition by alendronate
AUTHOR(S): Konttinen, Yrjo T.; Salo, Tuula; Hanemaaijer, Roeland; Valleala, Heikki; Sorsa, Timo; Sutinen, Meeri; Ceponis, Arnoldas; Xu, Jing-Wen; Santavirta, Seppo; Teronen, Olli; Lopez-Otin, Carlos
CORPORATE SOURCE: Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland
SOURCE: Matrix Biology (1999), 18(4), 401-412
CODEN: MTBOEC; ISSN: 0945-053X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hypothesis of the present work was that the pannus tissue overlying the articular hard tissues has an aggressive phenotype and contains the newly discovered collagenase-3 and its endogenous inducers and activators. We therefore analyzed the eventual presence of collagenase-3 and its regulation at the pannus-cartilage junction. Collagenase-3 mRNA (in situ hybridization) and enzyme protein (ABC and immunofluorescence staining) were found in the pannocytes in the pannus-hard tissue junction. Inflammatory round cells associated with the critical interface contained TNF-α and IL-1β. These cytokines induced collagenase-3 secretion in cultured rheumatoid synovial fibroblasts. Procollagenase-3 activators, stromelysin-1, 72 kDa type IV collagenase/gelatinase and membrane-type 1-MMP, were also found in the pannus-hard tissue junction. Active collagenase-3 was inhibited with alendronate (IC50 = 500-750 μM). Collagenase-3, due to its substrate profile and local synthesis in a milieu favoring its activation, might play a major role in the degradation of cartilage type II and bone type I collagens. Alendronate, at concns. attainable in vivo, is able to inhibit collagenase-3. This might offer an option to control collagenase-3-mediated tissue destruction in rheumatoid **arthritis.**
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 37 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:601534 CAPLUS
TITLE: Arylsulphonamide hydroxamic acids as potent inhibitors of **MMP-13**
CORPORATE SOURCE: Pfizer Products, Inc.: WO9907675
SOURCE: Expert Opinion on Therapeutic Patents (1999), 9(9), 1303-1307
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pfizer has disclosed a series of phenoxyphenyl sulfonamide hydroxamic acids, containing Cα gem-disubstitution and a novel N-ethylcarboxylate moiety, which are potent inhibitors of matrix metalloproteinase-13 (**MMP-13**), an enzyme which has been implicated in such disease states as **cancer** and **arthritis.** The compds. are significantly selective (300-1000 fold) for **MMP-13**

vs. MMP-1, the inhibition of which is believed to be associated with clin. side effects with previous broad spectrum MMP inhibitors. The Pfizer compds. are equally or more selective than several current clin. candidates and may have favorable pharmacodynamic profiles.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:473511 CAPLUS

DOCUMENT NUMBER: 131:139010

TITLE: Broad antitumor and antiangiogenic activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials

AUTHOR(S): Shalinsky, D. R.; Brekken, J.; Zou, H.; McDermott, C. D.; Forsyth, P.; Edwards, D.; Margosiak, S.; Bender, S.; Truitt, G.; Wood, A.; Varki, N. M.; Appelt, K.

CORPORATE SOURCE: Departments of Pharmacology, Agouron Pharmaceuticals, Inc., San Diego, CA, 92121, USA

SOURCE: Annals of the New York Academy of Sciences (1999), 878(Inhibition of Matrix Metalloproteinases), 236-270
CODEN: ANYAA9; ISSN: 0077-8923

PUBLISHER: New York Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We studied AG3340, a potent metalloproteinase (MMP) inhibitor with pM affinities for inhibiting gelatinases (MMP-2 and -9), MT-MMP-1 (MMP-14), and collagenase-3 (**MMP-13**) in many tumor models. AG3340 produced dose-dependent pharmacokinetics and was well tolerated after i.p. (i.p.) and oral dosing in mice. Across human tumor models, AG3340 produced profound tumor growth delays when dosing began early or late after tumor implantation, although all established tumor types did not respond to AG3340. A dose-response relationship was explored in three models: COLO-320DM colon, MV522 lung, and MDA-MB-435 breast. Dose-dependent inhibitions of tumor growth (over 12.5-200 mg/kg given twice daily, b.i.d.) were observed in the colon and lung models; and in a third (breast), maximal inhibitions were produced by the lowest dose of AG3340 (50 mg/kg, b.i.d.) that was tested. In another model, AG3340 (100 mg/kg, once daily, i.p.) markedly inhibited U87 glioma growth and increased animal survival. AG3340 also inhibited tumor growth and increased the survival of nude mice bearing androgen-independent PC-3 prostatic tumors. In a sixth model, KKLS gastric, AG3340 did not inhibit tumor growth but potentiated the efficacy of Taxol. Importantly, AG3340 markedly decreased tumor angiogenesis (as assessed by CD-31 staining) and cell proliferation (as assessed by bromodeoxyuridine incorporation), and increased tumor necrosis and apoptosis (as assessed by hematoxylin and eosin and TUNEL staining). These effects were model dependent, but angiogenesis was commonly inhibited. AG3340 had a superior therapeutic index to the cytotoxic agents, carboplatin and Taxol, in the MV522 lung **cancer** model. In combination, AG3340 enhanced the efficacy of these cytotoxic agents without altering drug tolerance. Addnl., AG3340 decreased the number of murine melanoma (B16-F10) lesions arising in the lung in an i.v. metastasis model when given in combination with carboplatin or Taxol. These studies directly support the use of AG3340 in front-line combination chemotherapy in ongoing clin. trials in patients with advanced malignancies of the lung and prostate.

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 39 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:473504 CAPLUS

DOCUMENT NUMBER: 131:319357

TITLE: Fluorogenic MMP activity assay for plasma including MMPs complexed to α2-macroglobulin

10/ 075,073

AUTHOR(S): Beekman, B.; Drijfhout, J. W.; Ronday, H. K.; TeKoppele, J. M.
CORPORATE SOURCE: Gaubius Laboratory, TNO Prevention and Health, Leiden, Neth.
SOURCE: Annals of the New York Academy of Sciences (1999), 878(Inhibition of Matrix Metalloproteinases), 150-158
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Elevated MMP activities are implicated in tissue degradation in, e.g., **arthritis** and **cancer.** The present study was designed to measure MMP enzyme activity in plasma. Free active MMP is unlikely to be present in plasma: upon entering the circulation, active MMP is expected to be captured by the proteinase inhibitor α2-macroglobulin (α2M). Reconstituted **MMP-13**/α2M complex was unable to degrade collagen (MW 300,000) in contrast to the low-mol.-weight fluorogenic substrate (MW <1500). Limited access of high-MW substrates to the active site of MMPs captured by α2M presents the most likely explanation. Consistently, the high-MW inhibitor TIMP (MW .apprx.28,000) was unable to inhibit MMP/α2M enzyme activity, whereas the low-MW inhibitor BB94 (MW .apprx.500) effectively suppressed enzyme activity. By using fluorogenic substrates with Dabcyl/Fluorescein as quencher/fluorophore combination, sensitive MMP-activity assays in plasma were achieved. Spiking of active **MMP-13** and **MMP-13**/α2M complex, and inhibitor studies with TIMP-1 and BB94, indicated that active MMPs are efficiently captured by α2M in plasma. MMP activity was even detected in control plasma, and was significantly increased in plasma from rheumatoid **arthritis** patients.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 40 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:404856 CAPLUS
DOCUMENT NUMBER: 131:63507
TITLE: Methods and compositions for improving the success of cell transplantation in a host
INVENTOR(S): Tremblay, Jacques P.
PATENT ASSIGNEE(S): Universite Laval, Can.
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9930730	A1	19990624	WO 1998-CA1176	19981215
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9918649	A1	19990705	AU 1999-18649	19981215

PRIORITY APPLN. INFO.:
CA 1997-2224768 19971215
CA 1997-2225837 19971224
WO 1998-CA1176 19981215

10/ 075,073

AB The present invention covers significant improvements for each event involved in the transplantation success or graft survival. These improvements, sep. or combined with each other, greatly ameliorate the recovery of a tissue towards a normal function. They comprise: (a) the reduction of early death of transplanted cells by anti-inflammatory agents such as TGFbeta1, an inhibitor of oligosaccharide synthesis, a glucosidase, IL-10, vIL-10, IL-4, INFgamma, IL-2R, IL-1Ra, Fas-L, sCR1, a super oxide dismutase, a neutrophil inhibitory factor (NIF), a ligand binding in an antagonist fashion to LFA-1, MAC-1, ICAM-1, CD-18, CD-31, CD-50, E-selectin, P-selectin, TNFalpha, IL-1 and IL-8. The anti-inflammatory agents may comprise an anti-LFA-1 or -ICAM-1; (b) the improvement of the diffusion and of the fusion of transplanted cells with the host tissue by metalloproteases; (c) the ex vivo proliferation of the transplanted cells with growth factors or oncogenes; (d) the use of fibroblasts or stem cells in lieu of myoblasts, by transforming the formers into the latter with myogenic genes; (e) expressing utrophin in lieu of dystrophin in cases of muscular dystrophy; and (f) immunosuppressing the host for long-term graft survival.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 41 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:398997 CAPLUS

DOCUMENT NUMBER: 131:196172

TITLE: Characterization of matrix metalloproteinases produced by rat alveolar macrophages

AUTHOR(S): Gibbs, Douglas F.; Warner, Roscoe L.; Weiss, Stephen J.; Johnson, Kent J.; Varani, James

CORPORATE SOURCE: Departments of Pathology and Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, 48109-0602, USA

SOURCE: American Journal of Respiratory Cell and Molecular Biology (1999), 20(6), 1136-1144
CODEN: AJRBEL; ISSN: 1044-1549

PUBLISHER: American Lung Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Evidence presented in the accompanying article (Gibbs, D. F., T. P. Shanley, R. L. Warner, H. S. Murphy, J. Varani, and K. J. Johnson. 1999. Role of matrix metalloproteinases in models of macrophage-dependent acute lung injury: evidence for alveolar macrophage as source of proteinases. Am. J. Respir. Cell Mol. Biol. 20:1145-1154) implicates alveolar macrophage matrix metalloproteinases (MMPs) in two models of acute lung **inflammation** in the rat. As a prerequisite to understanding which specific MMPs might be involved in the injury and how they might function, it was necessary to know the spectrum of enzymes present. To this end, alveolar macrophages were obtained from normal rat lungs by bronchoalveolar lavage, placed in culture with and without various agonists, and assessed by a variety of techniques for MMPs. The identification process involved characterization by gelatin, β-casein, and κ-elastin zymog., with confirmation of identity by Western blot/immunopptn. Message levels of detected MMPs were assessed by Northern blot. Rat alveolar macrophages were found to produce a low constitutive level of MMP-2 (72 kDa gelatinase A) that was only modestly upregulated following stimulation with phorbol myristate acetate, bacterial lipopolysaccharide, or IgA-containing immune complexes. Although control cells were found to produce little or no MMP-9 (92 kDa gelatinase B) or MMP-12 (metalloelastase), both enzymes were markedly upregulated upon stimulation. In the same stimulated macrophages there was little activity against type I collagen (associated with **MMP-13** [collagenase-3] on the basis of Western blotting), no activity suggestive of stromelysin or matrilysin, and no measurable secretion of the serine proteinases, elastase and cathepsin G. These data demonstrate the ability

of rat alveolar macrophages to elaborate certain MMPs under proinflammatory conditions, consistent with their possible involvement in the progression of acute **inflammation.**

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 42 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:243970 CAPLUS
DOCUMENT NUMBER: 131:49407
TITLE: Matrix metalloproteinases and tissue inhibitors of metalloproteinases in joint fluid of the patients with loose artificial hip joints
AUTHOR(S): Takei, Isao; Takagi, Michiaki; Santavirta, Seppo; Ida, Hideo; Hamasaki, Makoto; Ishii, Masaji; Fukushima, Shigenobu; Ogino, Toshihiko; Konttinen, Yrjo T.
CORPORATE SOURCE: Department of Orthopaedic Surgery, Yamagata University School of Medicine, Yamagata, 990-9585, Japan
SOURCE: Journal of Biomedical Materials Research (1999), 45(3), 175-183
CODEN: JBMRBG; ISSN: 0021-9304
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pseudojoint cavity formed in patients undergoing total hip arthroplasty (THA) is later remodeled to synovial membrane-like tissue, which produces pseudosynovial fluid. This pseudosynovium also is an important source of matrix metalloproteinases (MMPs). As it is widely speculated that synovial fluid MMPs may contribute to local tissue degradation in rheumatoid **arthritis** (RA) and osteoarthritis (OA), we hypothesize that locally produced MMPs are found in the pseudosynovial fluid, via which they have access to the implant-host interface, and that if they retain their proteolytic potential, they might contribute to aseptic loosening. ELISA, immunoblotting, and zymog. were used to analyze MMPs and tissue inhibitors of MMPs (TIMPs) in synovial fluid in aseptic loosening, which was compared to RA and OA. Pseudosynovial THA fluid was characterized using low levels of MMP-1 but moderate levels of **MMP -13** and MT1-MMP (MMP-14). Due to the lack of an appropriate assay, **MMP-13** and MT1-MMP were not similarly assessed, but the immunoblotting indicated that they were in the 56 kD intermediate proteolytically processed forms. The MMP-9 level was intermediate between RA and OA. MMP-2 was on a significant level, but there were no differences among study groups. The THA group also was characterized using relatively high levels of TIMP-1 and TIMP-2. Accordingly, MMP-9 and MMP-2 occurred in the 92 kD and 72 kD proenzyme form, resp., with full activity retained in all study groups. The data suggest that proMMP-2-TIMP-2 and proMMP-9-TIMP-1 complexes are formed in the pseudosynovial fluid due to the excess of TIMPs over MMPs in aseptic loosening of THA. TIMP-complexed MMPs are resistant to MMP-mediated proteolytic activation, which may explain their latency and proenzyme zymogen form. Thus, formation of stabilizing proMMP-TIMP complexes enable transportation of proMMPs far from their original site of production Due to motion-associated cyclic changes of the intra-articular pressure, fluid-phase MMPs stabilized by TIMPs might be absorbed to implant surfaces and interface tissues and help to dissect the implant/cement-to-bone interface in situ. Consequently, they may contribute to local proteolytic/tissue destructive events and aseptic loosening.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 43 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:47937 CAPLUS
DOCUMENT NUMBER: 130:265886
TITLE: Inhibition of interleukin-1α-induced cartilage

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oligomeric matrix protein degradation in bovine articular cartilage by matrix metalloproteinase inhibitors

AUTHOR(S): Ganu, Vishwas; Goldberg, Ronald; Peppard, Jane; Rediske, John; Melton, Richard; Hu, Shou-Ih; Wang, Weigwang; Duvander, Charlotte; Heinegard, Dick

CORPORATE SOURCE: Novartis Institute for Biomedical Research, Summit, NJ, USA

SOURCE: Arthritis & Rheumatism (1998), 41(12), 2143-2151
CODEN: ARHEAW; ISSN: 0004-3591

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors determined whether matrix metallo-proteinases (MMPs) degrade cartilage oligomeric matrix protein (COMP) to produce fragments similar to those found in synovial fluid (SF) from patients with **arthritis.** COMP fragments were generated in vitro by treating (a) bovine articular cartilage with interleukin-1α (IL-1α), (b) purified bovine COMP with MMPs, and (c) articular cartilage with MMPs. The fragments generated in each case were analyzed by Western blot, using an antibody to the C-terminal heptadecapeptide of COMP. IL-1α stimulation of cartilage resulted in a fragmentation of COMP, which was inhibited by MMP inhibitors CGS 27023A and BB-94. Isolated, recombinant MMPs rapidly degraded purified COMP, as well as COMP residing in cartilage. Several COMP fragments produced in vitro had similar electrophoretic mobility to those in SF of patients with **arthritis.** MMPs may contribute to the COMP fragments found in vivo. Quantitation of MMP-specific fragments may be useful in the evaluation of MMP inhibitors in patients with **arthritis.**

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 44 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:485187 CAPLUS

DOCUMENT NUMBER: 129:121650

TITLE: Monoclonal antibody against collagenase 3 and immunoassay method with the use of the same

INVENTOR(S): Tamei, Hironori; Azumano, Isao; Yoshida, Shin-ichi; Lopez-Otin, Carlos; Iwata, Kazushi

PATENT ASSIGNEE(S): Fuji Yakuhin Kogyo K. K., Japan

SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9829560	A1	19980709	WO 1997-JP4884	19971226

W: JP, US

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: JP 1996-356444 19961226

AB A method whereby latent **MMP-13** and active **MMP-13** can be sep. assayed with the use of an anti-**MMP-13** monoclonal antibody. The anti-**MMP-13** monoclonal antibody is prepared by using purified human pro-**MMP-13.** This antibody can be obtained in at least three types including one specifically binding to both of latent **MMP-13** and active **MMP-13**, one binding specifically to latent **MMP-13**, and one binding specifically to active **MMP-13.** Combined use of the monoclonal antibodies of these three types together with solid-phase antibodies,

enzyme-labeled antibodies (for example EIA), etc., makes it possible to sep. assay latent **MMP-13** and active **MMP-13**.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 45 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:400791 CAPLUS
DOCUMENT NUMBER: 129:160116
TITLE: Collagenase-3 (matrix metalloproteinase- 13) expression is induced in oral mucosal epithelium during chronic **inflammation**
AUTHOR(S): Uitto, Veli-Jukka; Airola, Kristiina; Vaalamo, Maarit; Johansson, Nina; Putnins, Edward E.; Firth, James D.; Salonen, Jukka; Lopez-Otin, Carlos; Saarialho-Kere, Ulpu; Kahari, Veli-Matti
CORPORATE SOURCE: Department of Oral Biological and Medical Sciences, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: American Journal of Pathology (1998), 152(6), 1489-1499
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Increased proliferation of mucosal epithelium during **inflammation** is associated with degradation of subepithelial connective tissue matrix and local invasion of the epithelial cells. Here we have studied, whether collagenase-3 (**MMP-13**), a collagenolytic matrix metalloproteinase with an exceptionally wide substrate specificity, is expressed in the epithelium of chronically inflamed mucosa. Examination of human gingival tissue sections from subjects with chronic adult periodontitis with in situ hybridization revealed marked expression of **MMP-13** in basal cells of some epithelial rete ridges expanding into connective tissue. Immunohistochem. staining demonstrated that these cells also expressed strongly laminin-5, suggesting that they are actively migrating cells. A strong signal for **MMP-13** mRNA was occasionally also noted in the suprabasal epithelial cells facing the gingival pocket, whereas no collagenase-1 (MMP-1) mRNA was detected in any areas of the epithelium. **MMP-13** expression was also detected in fibroblast-like cells associated with collagen fibers of the inflamed subepithelial connective tissue. In organ culture of human oral mucosa, **MMP-13** mRNA expression was observed in epithelial cells growing into connective tissue of the specimens. Regulation of **MMP-13** expression was examined in cultured normal nonkeratinizing epithelial cells isolated from porcine periodontal ligament. In these cells, **MMP-13** expression at the mRNA and protein level was potently enhanced (up to sixfold) by tumor necrosis factor-α, transforming growth factor-β1, and transforming growth factor-α and by keratinocyte growth factor in the presence of heparin. In addition, plating periodontal ligament epithelial cells on type I collagen stimulated **MMP-13** expression (sevenfold) as compared with cells grown on tissue culture plastic. The results of this study show, that expression of **MMP-13** is specifically induced in undifferentiated epithelial cells during chronic **inflammation** due to exposure to cytokines and collagen. Thus, it is likely that **MMP-13** expression is instrumental in the subepithelial collagenolysis and local invasion of the activated mucosal epithelium into the connective tissue.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 46 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

10/ 075,073

ACCESSION NUMBER: 1998:383219 CAPLUS
DOCUMENT NUMBER: 129:120952
TITLE: Collagenase-3 induction in rat lung fibroblasts requires the combined effects of tumor necrosis factor-α and 12-lipoxygenase metabolites: a model of macrophage-induced, fibroblast-driven extracellular matrix remodeling during inflammatory lung injury
AUTHOR(S): Mariani, Thomas J.; Sandefur, Stephanie; Roby, Jill D.; Pierce, Richard A.
CORPORATE SOURCE: Department of Internal Medicine, Washington University School of Medicine at Barnes-Jewish Hospital, St. Louis, MO, 63110, USA
SOURCE: Molecular Biology of the Cell (1998), 9(6), 1411-1424
CODEN: MBCEEV; ISSN: 1059-1524
PUBLISHER: American Society for Cell Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanisms responsible for the induction of matrix-degrading proteases during lung injury are ill defined. Macrophage-derived mediators are believed to play a role in regulating synthesis and turnover of extracellular matrix at sites of **inflammation.** We find a localized increase in the expression of the rat interstitial collagenase (**MMP-13**; collagenase-3) gene from fibroblastic cells directly adjacent to macrophages within silicotic rat lung granulomas. Conditioned medium from macrophages isolated from silicotic rat lungs was found to induce rat lung fibroblast interstitial collagenase gene expression. Conditioned medium from primary rat lung macrophages or J774 monocytic cells activated by particulates in vitro also induced interstitial collagenase gene expression. Tumor necrosis factor-α (TNF-α) alone did not induce interstitial collagenase expression in rat lung fibroblasts but did in rat skin fibroblasts, revealing tissue specificity in the regulation of this gene. The activity of the conditioned medium was found to be dependent on the combined effects of TNF-α and 12-lipoxygenase-derived arachidonic acid metabolites. The fibroblast response to this conditioned medium was dependent on de novo protein synthesis and- involved the induction of nuclear activator protein-1 activity. These data reveal a novel requirement for macrophage-derived 12-lipoxygenase metabolites in lung fibroblast MMP induction and provide a mechanism for the induction of resident cell MMP gene expression during inflammatory lung processes.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 47 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:362155 CAPLUS
DOCUMENT NUMBER: 129:146090
TITLE: One-step sandwich enzyme immunoassays for human matrix metalloproteinase 13 (collagenase-3) using monoclonal antibodies
AUTHOR(S): Tamei, Hironori; Azumano, Isao; Iwata, Kazushi; Yoshihara, Yasuo; Lopez-Otin, Carlos; Vizoso, Francisco; Knauper, Vera; Murphy, Gillian
CORPORATE SOURCE: Biopharmaceutical Department, Fuji Chemical Industries, Ltd., Takaoka, Japan
SOURCE: Connective Tissue (1998), 30(1), 15-22
CODEN: COTIE7; ISSN: 0916-572X
PUBLISHER: Japanese Society for Connective Tissue Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two one-step sandwich enzyme immunoassay (EIA) systems for human matrix metalloproteinase 13 (**MMP-13**, collagenase 3) have been established with two pairs of monoclonal antibodies prepared against human

recombinant proMMP-13. One was for proMMP-13 and the other was for both proMMP-13 and active **MMP-13**. **MMP-13** in samples simultaneously reacted with both solid-phase and peroxidase-labeled antibodies. The sensitivities of these EIA systems were 50 pg/mL (0.83 pg/well) and 80 pg/mL (1.3 pg/well) and linearity was obtained between 0.13 and 16 ng/mL (2.1-267 pg/well) as human proMMP-13 in both EIA systems, resp. **MMP-13** was detected in some serum and synovial fluids from the patients with rheumatoid **arthritis** (RA) and osteoarthritis (OA), but not **MMP-13** level of serum from normal subjects and patients with breast **cancer** was below the detection limits of these assay systems. Immunoreactivity anal. showed that **MMP-13** species in RA synovial fluid exists in a precursor form but not in a complex form with tissue inhibitor of metalloprotease-1 (TIMP-1).

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 48 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:320412 CAPLUS
DOCUMENT NUMBER: 129:103926
TITLE: Functional sites of chemically modified tetracyclines: inhibition of the oxidative activation of human neutrophil and chicken osteoclast pro-matrix metalloproteinases
AUTHOR(S): Sorsa, Timo; Ramamurthy, Nungavaram S.; Vernillo, Anthony T.; Zhang, Xia; Konttinen, Yrjo T.; Rifkin, Barry R.; Golub, Lorne M.
CORPORATE SOURCE: Departments of Medical Chemistry, Periodontology, Surgery, Anatomy, and Medicine, Institute of Dentistry, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
SOURCE: Journal of Rheumatology (1998), 25(5), 975-982
CODEN: JRHUA9; ISSN: 0315-162X
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We studied the relative ability of 6 different chemical modified non-antimicrobial analogs of tetracycline (CMT) to inhibit human and chicken matrix metalloproteinases (MMP) in vitro. The ability of tetracycline and its analogs to inhibit MMP appears to depend on the Ca++/Zn++ binding site at C11 (carbonyl oxygen) and C12 (OH group) of the mol., which is lacking in CMT-5, the pyrazole derivative of tetracycline. This significant property of CMT-5 was used to differentiate between the effects of CMT on already active MMP vs. the oxidative activation of latent MMP (pro-MMP). Cultured chicken osteoclast conditioned medium and purified human neutrophil progelatinase (MMP-9) and pro-collagenase (MMP-8) were assayed for proteinase activities using gelatin and collagen, resp. The pro-MMP were activated either by preincubation with 1 mM aminophenylmercuric acetate (APMA) or 100 μM sodium hypochlorite (NaOCl). CMT were added either to the preincubation mixts. together with NaOCl or after activation of pro-MMP with NaOCl. All CMT tested, except CMT-5, inhibited APMA or NaOCl activated pro-MMP. However, CMT-5 (like the other CMT), inhibited the oxidative activation of pro-MMP by NaOCl when added together by scavenging the reactive oxygen species. The degradation of type-I collagen by chicken osteoclast conditioned medium was probably due to MMP-2 and/or **MMP-13**. Oxidative activation of pro-MMP may be crucial during soft tissue/bone destruction in the inflammatory diseases, including the arthritides. Our results indicate that the Ca++/Zn++ binding site of CMT is not essential for inhibition of the oxidative activation of pro-MMP.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4 ANSWER 49 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:286365 CAPLUS
DOCUMENT NUMBER: 129:66340
TITLE: Distinct expression profiles of stromelysin-2 (MMP-10), collagenase-3 (**MMP-13**), macrophage metalloelastase (MMP-12), and tissue inhibitor of metalloproteinases-3 (TIMP-3) in intestinal ulcerations
AUTHOR(S): Vaalamo, Maarit; Karjalainen-Lindsberg, Marja-Liisa; Puolakkainen, Pauli; Kere, Juha; Saarialho-Kere, Ulpu
CORPORATE SOURCE: Department of Dermatology, University Central Hospital, University of Helsinki, Helsinki, 00250, Finland
SOURCE: American Journal of Pathology (1998), 152(4), 1005-1014
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Programmed expression of matrix metalloproteinases is involved in wound healing in various organs. We have previously demonstrated enhanced expression of collagenase-1, stromelysin-1, matrilysin, and tissue inhibitor of metalloproteinases (TIMP-1) in gastrointestinal ulcerations. To further define the role of matrix-degrading enzymes and their inhibitors in intestinal **inflammation** and ulcerations, the expression of stromelysin-2 (MMP-10), collagenase-3 (**MMP-13**), macrophage metalloelastase (HME, MMP-12), and TIMP-3 mRNAs was studied using in situ hybridization and immunohistochem. in 38 samples representing ulcerative colitis, Crohn's disease, ischemic colitis, and normal intestine. As controls for normally healing intestinal wounds, 12 postoperative samples of rat exptl. jejunal anastomoses were also examined The colitis types studied did not essentially differ in their MMP expression. We found stromelysin-2 mRNA in laminin-5-pos. and Ki-67-neg. enterocytes bordering the ulcerations. HME was abundantly expressed by macrophages in the vicinity of shedding mucosal epithelium and beneath the necrotic surface of the ulcers. Collagenase-3 and TIMP-3 were expressed by fibroblast-like cells deeper in the remodeling intestinal wall. Expression for stromelysin-2 and collagenase-3 was observed in granulation tissue, but not the epithelium, of the rat anastomoses. Our results suggest a role for stromelysin-2 in epithelial migration and for metalloelastase in macrophage movement and epithelial cell shedding.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 50 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:241767 CAPLUS
DOCUMENT NUMBER: 129:63734
TITLE: Cloning of the gene for interstitial collagenase-3 (matrix metalloproteinase-13) from rabbit synovial fibroblasts: differential expression with collagenase-1 (matrix metalloproteinase-1)
AUTHOR(S): Vincenti, Matthew P.; Coon, Charles I.; Mengshol, J. Andrew; Yocum, Sue; Mitchell, Peter; Brinckerhoff, Constance E.
CORPORATE SOURCE: Department of Medicine, Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Biochemical Journal (1998), 331(1), 341-346
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cartilage, bone and the interstitial stroma, composed largely of the interstitial collagens, types I, II and III, are remodeled by three

members of the metalloproteinase (MMP) family, collagenase-1 (MMP-1), collagenase-2 (MMP-8) and collagenase-3 (**MMP-13**). MMP-1 and **MMP-13** may contribute directly to disease progression, since they are induced in patients with rheumatoid **arthritis** and osteoarthritis. The study of MMP-1 and **MMP -13** gene regulation in models of arthritic disease has been problematic because mice and rats, which are typically used, only possess a homolog of **MMP-13**. Here the authors show that in contrast with mice and rats, rabbits possess distinct genes homologous to human MMP-1 and **MMP-13**. Furthermore, rabbit **MMP-13** is expressed simultaneously with MMP-1 in chondrocytes and synovial fibroblasts in response to the cytokines interleukin-1 and tumor necrosis factor-α, or the phorbol ester PMA. The time course of **MMP-13** induction is more rapid and transient than that of MMP-1, suggesting that distinct mechanisms regulate the expression of these two collagenases. The authors have cloned the rabbit **MMP-13** gene from synovial fibroblasts and demonstrated that the rabbit gene shares greater homol. with human **MMP-13** than does the mouse interstitial collagenase. Together with the fact that mice and rats do not possess a homolog to human MMP-1, these data suggest that the rabbit provides an appropriate model for studying the roles of interstitial collagenases in connective-tissue diseases, such as rheumatoid **arthritis** and osteoarthritis.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 51 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:126235 CAPLUS
DOCUMENT NUMBER: 128:192938
TITLE: Preparation of peptidyl compounds having MMP and TNF inhibitory activity
INVENTOR(S): Baxter, Andrew Douglas; Montana, John Gary
PATENT ASSIGNEE(S): Chiroscience Limited, UK
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9806696	A1	19980219	WO 1997-GB2149	19970808
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9738578	A1	19980306	AU 1997-38578	19970808
ZA 9707100	A	19980811	ZA 1997-7100	19970808
EP 925281	A1	19990630	EP 1997-935682	19970808
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

PRIORITY APPLN. INFO.: GB 1996-16643 19960808
WO 1997-GB2149 19970808
OTHER SOURCE(S): MARPAT 128:192938
AB Peptidyl compds. R3SCHR4XNR5CHRYNR1R2 [X = CO, CS; Y = CO, CS, SO, or SO2; R = substituted aryl, heteroaryl, aryl- or heteroarylalkyl; R1, R2 = H, alkyl; R3 = H, acyl; R4, R5 = H, (un)substituted alkyl, aryl, heteroaryl, or cycloalkyl] were prepared for use as MMP and TNF inhibitors. Thus,

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(S)-[2-(acetylthio)-5-phthalimidopentanoyl]-(S)-2-naphthylalanine N-methylamide was prepared via coupling of (S)-[(1,1-dimethylethoxy)carbonyl]-2-naphthylalanine N-methylamide with (S)-2-(acetylthio)-5-phthalimidopentanoic acid.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 52 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:39936 CAPLUS
DOCUMENT NUMBER: 128:162849
TITLE: In vitro sensitivity of the three mammalian collagenases to tetracycline inhibition: relationship to bone and cartilage degradation
AUTHOR(S): Greenwald, R. A.; Golub, L. M.; Ramamurthy, N. S.; Chowdhury, M.; Moak, S. A.; Sorsa, T.
CORPORATE SOURCE: Dep. Med. (Rheumatology), Long Island Jewish Medical Cent., New Hyde Park, NY, USA
SOURCE: Bone (New York) (1998), 22(1), 33-38
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There are at least nine tetracycline (TC) analogs (both antimicrobial and nonantimicrobial) with documented capacity to inhibit, both in vitro and in vivo, the connective tissue degrading activity of matrix metalloproteinases (MMPs). Of the three MMPs that can degrade native helical collagens, **MMP-13** (initially identified as rat osteoblast and human breast **cancer** collagenase, and now known to also be expressed by human cartilage and bone cells) is the most sensitive to TC inhibition (IC50 values in vitro generally less than 1 μg/mL); the TCs inhibit both the collagenolytic as well as the gelatinolytic activity of this enzyme. The IC50 for MMP-8 (neutrophil collagenase) in vitro ranges from 15 to 86 μg/mL depending on assay conditions and choice of TC, whereas inhibition of the fibroblast enzyme (MMP-1) generally requires levels in excess of 200 μg/mL (except for CMT-3). The TC compds. that are highly effective against **MMP-13** in vitro are also highly inhibitory of glycosaminoglycan release from interleukin-1-stimulated cartilage explants in culture. The current data correlate well with: (i) literature values for TC inhibition of bone resorption by isolated osteoclasts; (ii) inhibition by TCs of avian tibial resorption in organ culture; and (iii) the dramatic ability of TCs to inhibit bone destruction in many rat models (rats have only MMP-8 and **MMP-13**, and no MMP-1). By carefully selecting a TC-based MMP inhibitor and controlling dosages, it should be possible to inhibit pathol. excessive MMP-8 and/or **MMP-13** activity, especially that causing bone erosion, without affecting the constitutive levels of MMP-1 needed for tissue remodeling and normal host function; in this regard, three newly developed CMTs (especially CMT-8 and, to a lesser extent, CMT-3 and -7) appear to be most effective.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 53 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:39833 CAPLUS
DOCUMENT NUMBER: 128:175831
TITLE: In vitro sensitivity of the three mammalian collagenases to tetracycline inhibition: relationship to bone and cartilage degradation
AUTHOR(S): Greenwald, R. A.; Golub, L. M.; Ramamurthy, N. S.; Chowdhury, M.; Moak, S. A.; Sorsa, T.
CORPORATE SOURCE: Dep. Med. (Rheumatology), Long Island Jewish Med. Cent., New Hyde Park, NY, USA
SOURCE: Bone (New York) (1998), 22(1), 33-38

10/ 075,073

CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There are at least nine tetracycline (TC) analogs (both antimicrobial and nonantimicrobial) with documented capacity to inhibit, both in vitro and in vivo, the connective tissue degrading activity of matrix metalloproteinases (MMPs). Of the three MMPs that can degrade native helical collagens, **MMP-13** (initially identified as rat osteoblast and human breast **cancer** collagenase, and now known to also be expressed by human cartilage and bone cells) is the most sensitive to TC inhibition (IC50 values in vitro generally less than 1 μg/mL); the TCs inhibit both the collagenolytic as well as the gelatinolytic activity of this enzyme. The IC50 for MMP-8 (neutrophil collagenase) in vitro ranges from 15 to 86 μg/mL depending on assay conditions and choice of TC, whereas inhibition of the fibroblast enzyme (MMP-1) generally requires levels in excess of 200 μg/mL (except for 6-demethyl-6-deoxy-4-dedimethylaminotetracycline). The TC compds. that are highly effective against **MMP-13** in vitro are also highly inhibitory of glycosaminoglycan release from interleukin-1-stimulated cartilage explants in culture. The current data correlate well with: (i) literature values for TC inhibition by TCs of avian tibial resorption in organ culture; and (iii) the dramatic ability of TCs to inhibit bone destruction in many rat models (rats have only MMP-8 and **MMP-13**, and no MMP-1). By carefully selecting a TC-based MMP inhibitor and controlling dosages, it should be possible to inhibit pathol. excessive MMP-8 and/or **MMP-13** activity, especially that causing bone erosion, without affecting the constitutive levels of MMP-1 needed for tissue remodeling and normal host function; in this regard, three newly developed chemical-modified tetracyclines appear to be most effective.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 54 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:748013 CAPLUS
DOCUMENT NUMBER: 128:137846
TITLE: Highly increased levels of active stromelysin in rheumatoid synovial fluid determined by a selective fluorogenic assay
AUTHOR(S): Beekman, Bob; van El, Benno; Drijfhout, Jan Wouter; Ronday, H. Karel; TeKoppele, Johan M.
CORPORATE SOURCE: TNO Prevention and Health, Gaubius Laboratory, Department of Vascular and Connective Tissue Research, 2301 CE Leiden, 2215, Neth.
SOURCE: FEBS Letters (1997), 418(3), 305-309
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Stromelysin-1 (MMP-3) is an important member of the matrix metalloproteinase family. In joint-degrading diseases like **arthritis**, elevated levels of MMP-3 protein are detected in synovial fluid using immunol. methods. However, these methods do not discriminate between active and inactive enzyme. In the present study, a specific stromelysin activity assay was developed using the selective fluorogenic substrate TNO003 [Dabcyl-Gaba-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Glu(EDANS)-Ala-Lys-NH2], with cleavage at the Glu-Nva bond. For its use in biol. media, cleavage of TNO003 by enzymes other than stromelysin was effectively blocked by a proteinase inhibitor cocktail. Spiking of MMP-3 to synovial fluid resulted in an MMP-3 concentration-dependent linear increase in activity. The measured MMP-3 activity was not affected by the addition of **MMP-13**, even in a 5-fold excess over MMP-3.

Synovial fluid from rheumatoid **arthritis** patients demonstrated 100-fold higher levels of active stromelysin than control synovial fluids.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 55 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:729406 CAPLUS
DOCUMENT NUMBER: 128:21267
TITLE: Regulation of collagenase-3 expression in human breast carcinomas is mediated by stromal-epithelial cell interactions
AUTHOR(S): Uria, Jose A.; Stahle-Backdahl, Mona; Seiki, Motoharu; Fueyo, Antonio; Lopez-Otin, Carlos
CORPORATE SOURCE: Departmento de Bioquimica y Biologia Molecular, Facultad de Medicina, Universidad de Oviedo, Oviedo, 33006, Spain
SOURCE: Cancer Research (1997), 57(21), 4882-4888
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Collagenase-3 (**MMP-13**) is a recently identified member of the human matrix metalloproteinase gene family that is expressed in breast carcinomas and in articular cartilage from arthritic patients. Here, we have studied the cellular origin of this enzyme in breast carcinomas by in situ RNA hybridization, and we found that collagenase-3 is expressed by stromal cells immediately adjacent to epithelial tumor cells but not by the tumor cells themselves; nor is it expressed by the normal breast glandular epithelium. Consistent with this observation, coculture expts. using human fibroblasts and MCF-7 breast **cancer** cells revealed that conditioned medium from breast **cancer** cells stimulated the fibroblastic expression of collagenase-3 mRNA. In contrast, no stimulatory effect was observed when medium from fibroblast cells was added to breast **cancer** cells. These results strongly suggest that transcription of collagenase-3 in stromal cells is activated by diffusible factors released from epithelial breast **cancer** cells. A survey of a series of cytokines and growth factors known for their ability to induce collagenase-3 expression in human fibroblasts identified interleukin-1α and interleukin-1β as potential candidates for inducing the expression of this MMP gene in breast carcinomas. According to these results, collagenase-3 should be included among the mol. factors that are detected during the stromal reaction to invasive breast **cancer** and that, by concerted action, may be essential for tumor growth and progression.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 56 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:711632 CAPLUS
DOCUMENT NUMBER: 127:326202
TITLE: A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and specific collagenases in gingival crevicular fluid during adult periodontitis
AUTHOR(S): Golub, L. M.; Lee, H. M.; Greenwald, R. A.; Ryan, M. E.; Sorsa, T.; Salo, T.; Giannobile, W. V.
CORPORATE SOURCE: School Dental Medicine, State Univ. New York, Stony Brook, NY, 11794, USA
SOURCE: Inflammation Research (1997), 46(8), 310-319
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser
DOCUMENT TYPE: Journal
LANGUAGE: English

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AB It was determined whether an inhibitor of matrix metalloproteinases (MMPs), administered to human subjects in a dental school research clinic, can reduce bone-type collagen degradation fragments in oral inflammatory exudates containing excessive levels of collagenase. Gingival crevicular fluid (GCF) was collected from 18 subjects with adult periodontitis whose clin. findings (gingival **inflammation**, pocket depth, and bone loss on radiographs) predicted excessive MMP activity in their periodontal pockets. One month before the baseline appointment, plaque and calculus were removed from the teeth by supra-and subgingival scaling. After collection of GCF from 8-12 pocket sites per subject and recording of clin. indexes, 12 of the 18 subjects were treated with doxycycline at a low dosage (20 mg b.i.d.) known via an extensive literature to suppress mammalian MMP activity by a non-antimicrobial mechanism. The remaining 6 subjects were followed without drug treatment. At the baseline, 1 and 2-mo appointments, GCF samples were analyzed for ICTP (carhoxyterminal peptide, a pyridinoline-containing fragment of Type I collagen) and osteocalcin by RIA, as well as collagenolytic enzyme activity and MMP species. GCF ICTP and functional collagenase activity (but not osteocalcin levels) were reduced in the doxycycline-treated subjects at both 1 and 2 mo evaluations; there was no such change in the non-treated subjects. Western blots revealed that neutrophil-type collagenase (MMP-8) was the predominant MMP; **MMP-13**, which was associated with pathol. collagenolysis including bone resorption, was detected in human GCF for the 1st time and was more substantially reduced than MMP-8. This is the 1st demonstration in human subjects of the simultaneous reduction of excessive MMP activity with concomitant reduction in levels of collagen degradation fragments. The findings are potentially applicable to a wide variety of human diseases characterized by excessive collagenase activity.

L4 ANSWER 57 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:622368 CAPLUS
DOCUMENT NUMBER: 127:216912
TITLE: Activation of progelatinase B (proMMP-9) by active collagenase-3 (**MMP-13**)
AUTHOR(S): Knauper, Vera; Smith, Bryan; Lopez-Otin, Carlos; Murphy, Gillian
CORPORATE SOURCE: Strangeways Research Laboratory, Department of Cell and Molecular Biology, Cambridge, CB1 4RN, UK
SOURCE: European Journal of Biochemistry (1997), 248(2), 369-373
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human progelatinase B was activated by collagenase-3 in a time-dependent fashion. Activation proceeded through an intermediate form of 86 kDa to the final active form of 82 kDa. N-terminal amino acid sequence determination demonstrated that the Glu-40-Met-41 peptide bond was initially hydrolyzed followed by cleavage of the Arg-87-Phe-88 bond releasing the rest of the propeptide domain which was accompanied by the achievement of maximal enzymic activity as revealed using a quenched fluorescent substrate. Kinetic anal. of activation revealed that the rates were dependent on the concentration of the proenzyme as well as active collagenase-3. Active gelatinase B did not contribute to the activation rate of the proenzyme initiated by collagenase-3 and the results indicated that progelatinase B activation proceeds via bimol. cleavage with collagenase-3 involving sequential cleavage of the propeptide in 2 steps. The activation rates were not dependent on C-terminal domain interactions between progelatinase B and collagenase-3, as assessed using wild-type and C-terminal deletion mutants of both enzymes. Since elevated levels of both gelatinase B and collagenase-3 have been observed in **arthritis** and breast **cancer** pathol. these enzymes may well form a proteolytic cascade in these diseases which allows rapid turnover of the extracellular matrix.

L4 ANSWER 58 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:567757 CAPLUS
DOCUMENT NUMBER: 127:233026
TITLE: Matrix metalloproteinase 13 (collagenase 3) in human rheumatoid synovium
AUTHOR(S): Lindy, Otso; Konttinen, Yrjo T.; Sorsa, Timo; Ding, Yanli; Santavirta, Seppo; Ceponis, Arnoldas; Lopez-Otin, Carlos
CORPORATE SOURCE: University of Helsinki, Helsinki, FIN-00014, Finland
SOURCE: Arthritis & Rheumatism (1997), 40(8), 1391-1399
CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To show the eventual presence and extent of production of matrix metalloproteinase 13 (**MMP-13**, or collagenase 3) in rheumatoid synovial tissue samples and exts., and to assess the inhibition characteristics of recombinant **MMP-13**. Immunohistochem. avidin-biotin-peroxidase complex staining/morphometry was used to analyze **MMP-13**-pos. cells in situ. Neutral salt extraction of synovial tissue, electrophoresis of the extract in different buffer systems, and Western blotting were also used. The inhibitory properties of doxycycline, clodronate, pamidronate, and D-penicillamine for recombinant enzyme were determined with a soluble type II collagen assay. **MMP-13** was detected in fibroblast- and macrophage-like mononuclear cells in the synovial lining and stroma and in vascular endothelial cells. The overall expression of **MMP-13** in these cells in the synovial stroma was high in rheumatoid **arthritis** (86±12%) compared with osteoarthritis (17±5%) patient samples. In a high-pH native electrophoresis gel, immunoreactivity to anti-MMP-1 and anti-**MMP-13** were clearly separated, with anti-**MMP-13**-immunoreactive material. Finally, in contrast to MMP-1 and MMP-8, **MMP-13** was relatively resistant to the inhibitory effects of doxycycline and clodronate in vitro. Due to its localization in synovial tissue, its substrate profile, increased expression, and relative resistance to known MMP inhibitors, **MMP-13** is suggested to play a major role in the pathogenesis of tissue destruction in rheumatoid **arthritis**.

L4 ANSWER 59 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:360321 CAPLUS
DOCUMENT NUMBER: 127:79120
TITLE: Collagenase-3 (**MMP-13**) is expressed during human fetal ossification and re-expressed in postnatal bone remodeling and in rheumatoid **arthritis**
AUTHOR(S): Stahle-Baeckdahl, Mona; Sandstedt, Bengt; Bruce, Kerstin; Lindahl, Anders; Jimenez, Maria G.; Vega, Jose A.; Lopez-Otin, Carlos
CORPORATE SOURCE: Department of Dermatology, Karolinska Hospital, Stockholm, S-171 76, Swed.
SOURCE: Laboratory Investigation (1997), 76(5), 717-728
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To explore possible physiol. functions for the metalloproteinase collagenase-3, we have examined its temporal and spatial expression during human fetal development. Except for mesenchymal cells in the umbilical cord at 4 wk of gestation, signal for collagenase-3 mRNA was confined to mineralizing skeletal tissue and detected in hypertrophic chondrocytes and

osteoblastic cells involved in ossification beginning at 10 wk and continuing through gestation. These cells were also immunoreactive with collagenase-3 antiserum, indicating their ability to produce collagenase-3 protein. In osteoblastic cells, the expression of membrane-type 1 metalloproteinase and 75-kd gelatinase mRNA, which have the capacity to activate collagenase-3 in vitro, colocalized with that of collagenase-3. In postnatal tissues, collagenase-3 was re-expressed in processes involving skeletal remodeling, such as bone cysts and ectopic bone and cartilage formation. Multinucleated osteoclasts were consistently neg. for collagenase-3. Furthermore, in patients with seropos. rheumatoid **arthritis**, expression of collagenase-3 was prominent in articular cartilage, and collagenase-3 protein was detected by immunoblotting in synovial fluids. Consistent with its substrate specificities, a plausible function for collagenase-3 in these processes is to preferentially degrade type II collagen, thus serving a role during primary ossification, in skeletal remodeling, and in destructive joint disease.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 60 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:755602 CAPLUS

DOCUMENT NUMBER: 126:28536

TITLE: The helping hand of collagenase-3 (**MMP-13**): 2.7 Å crystal structure of its C-terminal haemopexin-like domain

AUTHOR(S): Gomis-Rueth, F. X.; Gohlke, U.; Betz, M.; Knaeuper, V.; Murphy, G.; Lopez-Otin, C.; Bode, W.

CORPORATE SOURCE: Max-Planck-Inst. Biochem., Planegg-Martinsreid, 82152, Germany

SOURCE: Journal of Molecular Biology (1996), 264(3), 556-566
CODEN: JMOBAK; ISSN: 0022-2836

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Collagenase-3 (**MMP-13**) is a matrix metalloproteinase involved in human breast **cancer** pathol. and in arthritic processes. Here, the crystal structure of its C-terminal haemopexin-like domain was solved by mol. replacement and refined to an R-value of 0.195 using data to 2.7 Å resolution This structure revealed a disk-like shape. The chain was folded into a β-propeller structure of pseudo-4-fold symmetry, with the 4 propeller blades arranged around a funnel-like tunnel. This central tunnel tube harbored 4 ions assigned as 2 Ca2+ and 2 Cl- ions. The C-terminal domain of collagenase-3 had a similar structure to the equivalent domain of gelatinase A and fibroblast collagenase 1; however, its detailed structure and surface charge pattern had a somewhat greater similarity to the latter, in agreement with the subgrouping of **MMP-13** with the collagenase subfamily of MMPs. It is proposed that several small structural differences may act together to confer the characteristic binding and cleavage specificities of collagenases for triple-helical substrates, probably in cooperation with a fitting interdomain linker.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 61 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:709341 CAPLUS

DOCUMENT NUMBER: 126:14923

TITLE: Modulation of matrix metalloprotease 13 (collagenase 3) gene expression in equine chondrocytes by interleukin 1 and corticosteroids

AUTHOR(S): Caron, John P.; Tardif, Ginette; Martel-Pelletier, Johanne; DiBattista, John A.; Geng, Changshan; Pelletier, Jean-Pierre

10/ 075,073

CORPORATE SOURCE: College Veterinary Medicine, Michigan State University, East Lansing, MI, 48824, USA
SOURCE: American Journal of Veterinary Research (1996), 57(11), 1631-1634
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Equine chondrocytes in monolayer culture were stimulated with rhIL-1β. Total RNA was extracted, purified, and reverse transcribed into DNA. Using appropriate primers, a putative **MMP-13** fragment was amplified by polymerase chain reaction, and cloned into a bacterial vector. The resultant fragment was purified and sequenced, then was used to prepare a digoxigenin-labeled cRNA probe. Monolayer cultures of first-passage chondrocytes were treated with rhIL-1β in the presence or absence of dexamethasone (10-6M) or methylprednisolone acetate (10-9M to 10-5M), in addition to pos. and neg. controls. Cellular RNA was extracted and resolved on agarose gels and subjected to northern blot anal., using the equine **MMP-13** probe. Reverse transcriptase-polymerase chain reaction enabled isolation of a 0.6-kb fragment of equine **MMP-13** cDNA that had 93% homol. with the human **MMP-13** cDNA sequence. RhIL-1 significantly stimulated **MMP-13** expression in the chondrocytes. Methylprednisolone acetate inhibited the stimulatory effects of rhIL-1 in dose-dependent manner that was statistically significant at 10-5M. Novel information was gained on the existence of **MMP-13** and its expression in equine chondrocytes, which suggests a possible role for this enzyme in matrix degradation in horses with **arthritis.**

L4 ANSWER 62 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:452513 CAPLUS
DOCUMENT NUMBER: 125:108639
TITLE: Cellular mechanisms for human procollagenase-3 (**MMP-13**) activation. Evidence that MT1-MMP (MMP-14) and gelatinase A (MMP-2) are able to generate active enzyme
AUTHOR(S): Knaeuper, Vera; Will, Horst; Lopez-Otin, Carlos; Smith, Bryan; Atkinson, Susan J.; Stanton, Heather; Hembry, Rosalind M.; Murphy, Gillian
CORPORATE SOURCE: Dep. Cell Mol. Biol., Strangeways Res. Lab., Worts' Causeway, Cambridge, CB1 4RN, UK
SOURCE: Journal of Biological Chemistry (1996), 271(29), 17124-17131
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gelatinase A and membrane-type metalloproteinase (MT1-MMP) were able to process human procollagenase-3 (Mr 60,000) to the fully active enzyme (Tyr85 N terminus; Mr 48,000). MT1-MMP activated procollagenase-3 via a Mr 56,000 intermediate (Ile36 N terminus) to 48,000 which was the result of the cleavage of the Glu84-Tyr85 peptide bond. We have established that the activation rate of procollagenase-3 by MT1-MMP was enhanced in the presence of progelatinase A, thereby demonstrating a unique new activation cascade consisting of three members of the matrix metalloproteinase family. In addition, procollagenase-3 can be activated by plasmin, which cleaved the Lys38-Glu39 and Arg76-Cys77 peptide bonds in the propeptide domain. Autoproteolysis then resulted in the release of the rest of the propeptide domain generating Tyr85 N-terminal active collagenase-3. However, plasmin cleaved the C-terminal domain of collagenase-3 which results in the loss of its collagenolytic activity. Con A-stimulated fibroblasts expressing MT1-MMP and fibroblast-derived plasma membranes

were able to process human procollagenase-3 via a Mr 56,000 intermediate form to the final Mr 48,000 active enzyme which, by analogy with progelatinase A activation, may represent a model system for in vivo activation. Inhibition expts. using tissue inhibitor of metalloproteinases, plasminogen activator inhibitor-2, or aprotinin demonstrated that activation in the cellular model system was due to MT1-MMP/gelatinase A and excluded the participation of serine proteinases such as plasmin during procollagenase-3 activation. We have established that progelatinase A can considerably potentiate the activation rate of procollagenase-3 by crude plasma membrane prepns. from Con A-stimulated fibroblasts, thus confirming our results using purified progelatinase A and MT1-MMP. This new activation cascade may be significant in human breast **cancer** pathol., where all three enzymes have been implicated as playing important roles.

L4 ANSWER 63 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:187785 CAPLUS
DOCUMENT NUMBER: 124:283007
TITLE: Cloning, expression, and type II collagenolytic activity of matrix metalloproteinase-13 from human osteoarthritic cartilage
AUTHOR(S): Mitchell, Peter G.; Magna, Holly A.; Reeves, Lisa M.; Lopresti-Morrow, Lori L.; Yocum, Sue A.; Rosner, Philip J.; Geoghegan, Kieran F.; Hambor, John E.
CORPORATE SOURCE: Central Research Division, Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Journal of Clinical Investigation (1996), 97(3), 761-8
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Proteolysis of triple-helical collagen is an important step in the progression toward irreversible tissue damage in osteoarthritis. Earlier work on the expression of enzymes in cartilage suggested that c collagenase-1 (MMP-1) contributes to the process. Degenerate reverse transcription polymerase chain reaction expts., Northern blot anal., and direct immunodetection have now provided evidence that collagenase-3 (**MMP-13**), an enzyme recently cloned from human breast carcinoma, is expressed by chondrocytes in human osteoarthritic cartilage. Variable levels of **MMP-13** mRNA were present in total RNA prepared from six osteoarthritic cartilage samples. Expression of both **MMP-13** and MMP-1 in cartilage was significantly induced at both the message and protein levels by interleukin-1α. Recombinant **MMP-13** cleaved type II collagen to give characteristic 3/4 and 1/4 fragments; however, **MMP-13** turned over type II collagen at least 10 times faster than MMP 1. Expts. with intact type II collagen as well as a synthetic peptide suggested that **MMP-13** cleaved type II collagen at the same bond as MMP-1, but this was then followed by a secondary cleavage that removed three amino acids from the 1/4 fragment amino terminus. The expression of **MMP-13** in osteoarthritic cartilage and its activity against type II collagen suggest that the enzyme plays a significant role in cartilage collagen degradation, and must consequently form part of a complex target for proposed therapeutic interventions based on collagenase inhibition.

L4 ANSWER 64 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:142628 CAPLUS
DOCUMENT NUMBER: 124:196970
TITLE: Degradation of cartilage aggrecan by collagenase-3 (**MMP-13**)
AUTHOR(S): Fosang, Amanda J.; Last, Karena; Knaeuper, Vera; Murphy, Gillian; Neame, Peter J.

10/ 075,073

CORPORATE SOURCE: Orthopaedic Molecular Biology Research Unit, Melbourne University Department of Paediatrics, Royal Children's Hospital, Parkville, 3052, Australia
SOURCE: FEBS Letters (1996), 380(1,2), 17-20
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The degradation of the large cartilage proteoglycan, aggrecan (I), in **arthritis** involves an unidentified enzyme aggrecanase (II), and at least one matrix metalloproteinase (MMP). Proteinase-sensitive cleavage sites in the I interglobular domain (IGD) have been identified for many of the human MMPs, as well as for II and other proteinases. The major MMP expressed by chondrocytes stimulated with retinoic acid to degrade their matrix was collagenase-3 (**MMP-13**). Because of its potential role in I degradation, the specificity of **MMP-13** for a I substrate was examined The results showed that **MMP-13** cleaved I in the IGD at the same site (..PEN341- FFG..) identified for other members of the MMP family, and also at a novel site (..VKP384-VFE..) not previously observed for other proteinases.

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(FILE 'HOME' ENTERED AT 14:29:28 ON 15 MAR 2004)

FILE 'CAPLUS' ENTERED AT 14:29:37 ON 15 MAR 2004
L1 665 S "MMP-13" OR METALOPROTEASE
L2 667 S "MMP-13" OR METALOPROTEASE?
L3 278 S L2 AND (CANCER? OR HEART? OR INFLAMMATION OR ARTHRITIS)
L4 64 S L3 NOT PY>2000

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